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THE NATURAL HISTORY OF HOMOZYGOUS SICKLE-CELL ANAEMIA IN CENTRAL AFRICA[1]

By H. C. TROWELL, A. B. RAPER, and H. F. WELBOURN

With Plate 41

Of all the genetically determined diseases of man, sickle-cell anaemia is probably the commonest. It owes this position to the remarkable circumstance that the gene, which in the homozygous state usually leads to a lethal anaemia, is beneficial to its carrier when in the heterozygous state, provided he is exposed to malarial infection (Brain, 1952; Allison, 1954; Raper, 1955, 1956). Thus over large tracts of tropical Africa, instead of the gene being eliminated or reduced to a frequency at which it could be maintained only by mutation, it is enabled under the influence of selection to attain quite high frequencies, so that it is often present in more than 20 per cent. of the population. This means that about one per cent. of the children born in many parts of this vast area are destined to develop sickle-cell anaemia. Vandepitte (1954) has estimated that in every generation of the inhabitants of tropical Africa there must be born about one million children who will be so affected. In the United States and parts of Central America the proportion, though much less, is still considerable; and in the other main foci of the abnormality, Greece and southern India, the proportion may be as high but the affected population is smaller.

That a paediatric problem of this magnitude existed in Africa has only recently been realized; many circumstances connected with medical practice in primitive tropical conditions have combined to conceal it. This alone makes it desirable that an account should be presented of the natural history of sickle-cell anaemia in Africa. But there is another consideration, relevant to the disease in all parts of the world. The current description is based upon the many excellent clinical and pathological accounts published in America between 1910 and 1949. But the series of discoveries that began with the work of Pauling, Itano, Singer, and Wells in 1949 (reviewed by Itano and his colleagues, 1955, 1956), has revealed eight or more hereditary variants of haemoglobin besides the normal (A), the foetal (F), and the sickle-cell type (S). These are known by the symbols C, D, E, G, H, I, J, K; they are inherited as simple Mendelian characters (except H), and in the heterozygous state with haemoglobin-A they usually account for some 20 to 50 per cent. of the subject's production of haemoglobin. They differ in their globin moieties, and are distinguishable chiefly by electrophoresis. The genes for haemoglobins S, C, and D are alleles of the normal type, and so probably are some of the others. In

[1] Received November 26, 1956.

addition, it is now known that an effect of the thalassaemia gene is to block the synthesis of normal haemoglobin. Some of these genes, especially those for haemoglobins C, D, and E, and for thalassaemia, are quite common in certain parts of the world, and all the latter except E have been encountered in anaemic patients together with the gene for sickling. Until electrophoretic analysis became generally used, such cases of 'double heterozygosity' would all have been characterized by their only obvious property, that of sickling, and so it is evident that the older descriptions may have referred to a group of related syndromes that are now distinguishable. In particular, it is known that a considerable number of cases previously thought to be sickle-cell anaemia in American Negroes can now be identified as haemoglobin-C:sickle-cell disease (Smith and Conley, 1954). Most of the previous reports from West Africa, also, must be read with the understanding that they probably contained many examples of anaemias associated with haemoglobin-C, for this variant is much commoner there than in America (Edington and Lehmann, 1954). The importance of this consideration lies in the fact that haemoglobin-C:sickle-cell disease is a much milder condition than true sickle-cell anaemia, with a later onset and a much greater expectation of life.

The recognition of sickle-cell anaemia was belated in those parts of tropical Africa where other haemoglobin variants do not occur. Except for one early record from the Sudan (Archibald, 1926), the disease escaped notice until it was described from Uganda (Trowell, 1945). A detailed description, based on 88 cases, which followed from the Belgian Congo (J. and C. Lambotte-Legrand, 1951), can likewise be assumed to refer to the homozygous anaemia, since no other haemoglobin variants occur there to any extent (Vandepitte and Colaert, 1955). It was noticed by the Belgian workers that the disease occurred at an earlier age, and evolved more rapidly, than appeared to be the case in American Negroes. No description yet published, however, has been limited to the proved homozygous anaemia. It is therefore our intention to describe the single entity, 'pure' or homozygous sickle-cell anaemia, for every patient described in the present communication was proved to possess no other variant of adult haemoglobin than haemoglobin-S.

Provenance of Cases, and Methods

The clinical part of this study was based on 59 cases of sickle-cell anaemia, all in persons of pure African descent. Thirty-eight cases were studied in Mulago Hospital, Kampala, Uganda, during 1954, the majority occurring in young children. Most of these patients were admitted because of symptoms referable to the developed disease, but a few were found from a survey conducted in the out-patient clinics (Raper, 1955), in which detection of cases was largely on haematological grounds. Twenty-one cases were discovered among African infants attending Child Welfare Clinics in and around Kampala (H. F. W.). Some of these had been observed for several years by the time of the present study, and this group contributed most of the few adolescent patients. In the

clinics, cases were detected sometimes in the same way as in hospital, sometimes on routine examination of the blood, and sometimes in families already known as proved or potential sources of homozygous children.

The pathological section of the study is based on five autopsies. Only two refer to members of the above clinical series; the other three complete the total number of autopsies performed by one of us (A. B. R.) in cases of sickle-cell anaemia during the period 1950 to 1955.

No clinical case has been accepted unless the diagnosis had been completed on haematological grounds. Besides the demonstration of a haemolytic anaemia, it was required that electrophoresis of the haemoglobin should show a single band in the position of haemoglobin-S. Electrophoresis was performed on paper, by the hanging-strip method, in veronal buffer at pH 8·6. Due account was taken of the fact that by this technique a single band of haemoglobin may be seen, between the positions of haemoglobins A and S, in the case of very small infants retaining considerable amounts of haemoglobin-F, although they may be heterozygous trait-carriers; final diagnosis was deferred until the characteristic pattern was recorded. Haemoglobin-D was not excluded by making solubility determinations; hence the combination S-D, if it had occurred in our series, would have escaped accurate diagnosis. But it has been shown (Jacob, 1955) that no haemoglobin-D could be detected in 500 Africans, with non-sickling blood, in the same population from which our patients were drawn.

The Incidence of Sickle-Cell Anaemia

It was at one time thought that sickle-cell anaemia was much rarer in Africans than among American Negroes (Raper, 1950), and this probably remains true as far as adult patients are concerned. But the work of Neel (1949) and Beet (1949), which established that the anaemia was due to the inheritance by a child of two genes for sickling, one from each parent, acted as a powerful stimulus to case-finding. J. and C. Lambotte-Legrand (1951) insisted that if very young children were examined the disease would be found with a frequency equal to that expected on genetic grounds, and later (1955) demonstrated that this in fact occurred in the environs of Léopoldville. Foy, Kondi, and Brass (1951) took a similar view in Kenya. Contrary views were expressed from time to time, but it is now generally agreed that the homozygous hypothesis gives an accurate expression of the number of cases that will be found, provided that the search is made among infants. Our own experience is in accord with this view. Among children attending Child Welfare Clinics around Kampala there are representatives of three main tribal groups that have different sickling rates, and the number of cases of sickle-cell anaemia detected among these children is shown in Table I. Similar figures, obtained among children attending a hospital clinic (for any cause) during a survey concerned with the incidence of malaria (Raper, 1955), are shown in Table II. These are of course not random samples. On the one hand, children attending medical centres would show more cases of anaemia than the general population; on the other hand, children up to

the age of 10 were included, thus diminishing the proportion of cases having an anaemia that is often fatal in early childhood. But the figures are representative of groups of children that might be encountered in paediatric practice in many centres in tropical Africa, and they show how closely, in practice, the observed approximates to the expected incidence.

TABLE I

Incidence of Sickle-Cell Anaemia in Child Welfare Clinics

Tribal group	*Number of children examined*	*Positive for sickling*		*Expected* cases of S.C.A.*	*Observed cases of S.C.A.*
		Number	*%*		
Ganda	953	158	16·27	6·9	15
Luo	294	60	20·4	3·42	5
Ruanda-Rundi	135	5	3·7	0·047	0

TABLE II

Incidence of Sickle-Cell Anaemia in Children Attending Hospital

Tribal group	*Number of children examined*	*Positive for sickling*		*Expected* cases of S.C.A.*	*Observed cases of S.C.A.*
		Number	*%*		
Ganda	758	130	17·2	7·29	8
Luo	196	41	20·9	2·37	3
Ruanda-Rundi	136	7	5·1	0·09	0

* Calculated on the assumption that the gene was distributed amongst the children of each tribal group according to the Hardy–Weinberg law.

Clinical Description

Onset

No case of sickle-cell anaemia has been observed in a newly born child, or in the first month or two of life. The anaemia can develop only when foetal haemoglobin is mostly replaced, not by the normal adult form, but by haemoglobin-S, a process that is normally complete in about the fifth month. By the sixth month the anaemia is easily recognizable, and most cases present themselves and are diagnosed in children between the ages of seven and 15 months. Occasionally diagnosis is possible at an earlier age. In their 300 cases the Lambotte-Legrands (1955) established the diagnosis three times before the age of three months, and our own series contains two cases diagnosed at the end of the third month, and a post-mortem diagnosis at the same age. Out of 22 of our cases in which reliable information was obtained concerning the onset of the disease, the parents had noticed signs of illness in 20 cases in the first year of life (three in the first trimester, 14 in the second, two in the third, and one in the fourth). In two cases the disease was apparently not noticed until the second and fourth years, but, as these two children were respectively eight and 10 years old when brought for examination, faulty memory may have supplied inaccurate data.

In the majority of our cases no clear history of the time or mode of onset could be obtained. This is because the development of symptoms is indeed very

gradual, and is not noticed by African mothers, who regard some degree of ill health, malaria, and 'fever' as a normal feature of infancy. Information upon the earliest events can only be obtained by careful observation of children from birth. This was achieved in the case of four infants attending Child Welfare Clinics from birth, who subsequently developed sickle-cell anaemia. No departure from the normal was detected clinically, or in the haemoglobin content

TABLE III

Events in the Onset of a Case of Sickle-Cell Anaemia

Age of child (weeks)	*Weight (kg.)*	*Haemoglobin (gm./100 ml.)*	*Blood morphology*	*Clinical events*
5½	4·41	8·3	Normal	Coryza
6½	4·82	..	Polychromasia	..
14½	6·07	..	Marked polychromasia	..
15½	6·16	..	S.C.A.	Electrophoresis shows SS pattern
18½	6·42	8·4	,,	Coryza, diarrhoea
19½	6·61	5·6	,,	..
24½	7·5	8·4	,,	Bilateral metacarpal swelling
25½	7·52	8·4	,,	Hands better
30½	7·58	7·0	,,	Jaundice, dark urine, vomiting, diarrhoea. Spleen palpable

or morphology of the blood, during the first month. At this time the appearance of the sickled erythrocytes gave no indication of the homozygous state, and electrophoretic diagnosis was impossible because of the presence of a large amount of haemoglobin-F. In each case the earliest change observable was a reduced haemoglobin level, together with an increase of polychromatic cells in the blood film. Shortly afterwards a mild anaemia became apparent clinically, and by this time the blood film usually revealed a leucocytosis and the presence of normoblasts. This state was reached at about the end of the third or fourth month, and supported a tentative diagnosis. Soon after these observations confirmation was obtained, either by the demonstration of the electrophoretic pattern of sickle-cell anaemia, or by the appearance of a characteristic swelling of the bones of the hands or feet. In the four cases mentioned the diagnosis was reached at the end of the third, third, fourth, and sixth month respectively. At this early stage doubt will always arise whether the changes are due to malaria, if there is any possibility of this infection. The symptoms of pallor and mild fever, and the early stages of the haemolytic anaemia, are indistinguishable from the same events in malaria; and indeed we have observed malaria superimposed on sickle-cell anaemia. Sometimes the decision has to be postponed for a month or more. In one of the above children any confusion with malaria was avoided. This child was one of a group being studied at a Welfare Clinic by Dr. M. D. Thompson, as part of a trial of amodiaquine ('camoquin') given weekly by mouth for the prophylaxis of malaria. Dr. Thompson examined the blood weekly, and noticed a low haemoglobin-content at five and a half weeks, and a slight increase in polychromasia at six and a half weeks. Subsequent findings are shown in Table III. In our experience, therefore, the diagnosis can

be suspected, and often proved, on haematological grounds before the appearance of distinctive clinical signs. This is especially so if it is already known that both parents are carriers of the sickle-cell gene.

Manifestations during the first two years of life (37 cases; six deaths)

Table IV shows the new cases detected at Child Welfare Clinics (19 cases; two deaths), and those diagnosed in children in hospital cases (18 cases; four deaths). The disease seldom attracted attention during the first six months of

TABLE IV

Cases in the first Two Years of Life

Age of children (months)	*Clinics*		*Hospital*	
	New cases	*Deaths*	*New cases*	*Deaths*
0–5+	4	0	0	0
6–11+	7	1	9	2
Died in 2nd year	..	1	..	0
12–23+	8	0	9	2
Total	19	2	18	4

life. Patients observed regularly in Child Welfare Clinics often looked surprisingly well: the anaemia was not severe, at least at first, and the symptoms were so mild, or resembled so closely those of malaria, that parents usually made no complaint, and medical personnel asked to see the child expressed doubts concerning the diagnosis. This was because, at this age, minor illness is so common, and in tropical countries repeated attacks of malaria are almost universal, so that some fever, anaemia, and splenomegaly are present in many infants. Moreover, many African children pass through a period of malnutrition during the second year of life (Trowell, Davies, and Dean, 1954), manifested as a failure of growth, oedema, diarrhoea, and a characteristic dermatosis. These signs appeared in five cases in the present series, and vomiting, inanition, and marasmus contributed to the death of one severely anaemic infant of seven months. Many other children with sickle-cell anaemia observed in Welfare Clinics were not growing well during the second year—the mean weight of those aged 16 to 20 months was only 7·8 kg.—and the anaemia, which was most severe at this period, appeared to aggravate the effects of both malnutrition and infections.

Anaemia was seldom at first a prominent sign, and might be concealed by the dark colour of the African skin, but it could be detected in the conjunctiva and finger-nails in a few children between six and 24 months old. By the sixth month the haemoglobin was usually 7 to 9 gm. per 100 ml. Thereafter lower figures were often found, especially in children in the second six months of life suffering an acute haemolytic episode (haemoglobin usually 2 to 6 gm. per 100 ml.); there were two fatal crises among these patients. Children attending the Welfare Clinics usually had less anaemia; for many months in succession they showed a fairly constant haemoglobin-content, often 6 to 8 gm. per 100 ml. Crises, at least of a severe degree, were relatively infrequent (see p. 412).

Fever was often denied, for reasons given above, but careful questioning by the doctor and intelligent co-operation by the parents elicited the fact that some fever occurred in all cases from time to time, and was by no means limited to the periods of manifest illness. Although a raised temperature was often not detected in an infant brought to a Child Welfare Clinic, all 18 in-patients showed periods of unexplained fever. It was seldom severe, but short incidents of low fever on the temperature chart corresponded with periods of slight malaise. Rarely high fever accompanied a haemolytic episode, as described later (p. 412). Leucocytosis was also a feature of the chronic haemolytic anaemia (Table VI) so that in many cases it was difficult either to detect or to exclude the presence of an intercurrent bacterial infection.

Jaundice. With the minor elevations of temperature there was usually no detectable jaundice but, if severe attacks of haemolysis occurred, yellowing of the sclerotics and darkening of the urine were noted. These signs were never seen before six months of age, but were seen at some time or other in six out of 20 children observed during the second half of the first year, and a history of these manifestations was obtained in eight out of 17 new cases seen during the second year of life. The episodes of jaundice were usually short in duration. The serum-bilirubin exceeded 1·0 mg. per 100 ml. in only seven out of 18 patients tested in the first two years of life.

Enlargement of liver and spleen. The spleen became palpable in 30 out of the 37 cases under the age of two years, and the liver was palpable to more than one finger's breadth below the right costal margin in six of these patients. Great enlargement of either organ was rare in infancy. During severe episodes of haemolysis and fever these organs might enlarge and become tender on palpation, but these signs decreased as the episodes passed.

The bones. A full discussion of the bony changes is given later (pp. 412–14). At an early stage in the evolution of the disease the bones of the fingers, hands, or feet are often affected in a striking and characteristic manner. At the Child Welfare Clinics six out of 11 children below 12 months of age, and five out of eight between the ages of 12 and 24 months, showed attacks of acute osteopathy of the hands. Affection of the feet was less often seen, but minor degrees would easily be missed in the more fleshy lower extremity. In our experience no other disease gives repeated swelling in the hands and feet of African infants.

Manifestations during later childhood (two to 12 years) (18 new cases, with 17 followed from the previous group; five deaths)

These 35 cases fell into two groups: first, children who were seen at frequent intervals at the Child Welfare Clinics (14 cases) and generally appeared fairly well, and second, those admitted to hospital (21 cases) because of some episode of illness due to sickle-cell anaemia. Those who survived the hazards which beset the onset of the haemolytic anaemia, and the malnutrition and infections that occurred in the danger period from six to 24 months, began to suffer less severely as they became older. The haemoglobin concentration rose slightly,

probably because the total volume of the bone-marrow was increasing proportionately to the body's needs.

Of the 14 children observed in Child Welfare Clinics, many over a period of several years, five appeared well and had no haemolytic crises. But nine had indifferent health for long periods, and four of these had fatal haemolytic crises, sometimes after a period of apparent good health. Most of the children who survived (10 cases), especially those from the upper social groups, grew well, and had a normal or only slightly subnormal weight; they were able to engage in a fair amount of physical activity, and their mean haemoglobin level was 9·4 gm. per 100 ml., apart from observations in manifest crises. Apart from crises, the haemoglobin was only twice recorded as below 7·0 gm. per 100 ml. in this group of children. They often looked well, and might pass as normal children, and episodes of severe illness became less severe in later childhood; limb pains, however, still occurred. Jaundice was not recorded in any of the four children in the third year of life, but after that age it was noted in all the remaining 10 cases. Usually it was mild, but it tended to be persistent; it was very severe in the fatal haemolytic crises. Splenomegaly was seldom a marked feature; of the 14 children, seven had no palpable enlargement of the spleen, in five the spleen could just be felt, and in two it could be felt two fingers' breadth below the rib margin. The liver was palpable in only three cases.

A somewhat different picture was presented by the 21 children admitted to hospital. They were suffering from one or other of the acute episodes that punctuated the course of apparently fair health. A severe haemolytic crisis was present in eight, of whom three died (two of these three had attended the Clinics regularly). A haemolytic crisis was not seen in a child aged more than seven years in the group under discussion (aged two to 12 years), and was seen only once in an adolescent. In eight of the hospital cases there was a history of frequent attacks of fever, and of pains and swellings in the limbs. In four cases there had been long periods of ill health, the child being seriously incapacitated, and more often ill than well. In three cases there was a history of attacks of severe and unexplained abdominal pain.

Manifestations during adolescence (12 to 18 years) (four new cases, and two from the previous group; no deaths)

Some details of the six adolescents are given in Table V. Only one child in this group, aged 13 years, suffered from frequent haemolytic crises; she had a haemoglobin level of 3·5 gm. per 100 ml., and great enlargement of the spleen (10 fingers' breadth below the left rib margin). In the other cases the haemoglobin was in the range 7·0 to 11·0 gm. per 100 ml., and there was no history of recent haemolytic crises. All six children were jaundiced, and the serum-bilirubin averaged 6·2 mg. per 100 ml. The jaundice was fairly constant in four patients; in the other two it was milder and more variable. Enlargement of the liver was present in all the more jaundiced children. Limb pains, often with little to demonstrate at clinical or radiological examination, remained a

complaint of all six patients, and continued to make regular schooling or employment almost impossible. Some had attacks of transient arthropathy resembling that occurring in acute rheumatism. One boy of 15 (referred to below) suffered from necrosis of the head of the femur. Although the normal range of physical development has been little studied in African adolescents, clinical observation and measurement (Table V) suggests that serious disturbances occurred in all six of these anaemic children. Most of them presented a thin physique, with

TABLE V

Adolescent Patients

Age (years)	*Sex*	*Height (cm.)*	*Weight (kg.)*	*Haemoglobin (gm./100 ml.)*	*Jaundice*	*Enlargement below costal margin (fingers' breadth) of*	
						Liver	*Spleen*
12	M	118	18·2	7·7	Severe, constant	2	3
13	F	123	20·5	3·5	,,	4	10
14	F	143	38·5	10·1	,,	3	0
15	M	152	34	9·6	Slight	0	3
16	F	156	38	10·6	,,	0	0
18	M	160	32·3	8·9	Severe	2	2

long, slender limbs, delicate hands, fingers, and feet, and a narrow trunk. They looked several years younger than their stated ages, and this difference was accentuated by the poor development of the secondary sex characteristics. All the boys had small flaccid testes. When these observations were made in 1954, none of the girls had menstruated, but subsequently menstruation began in two of them at the ages of 15 years 10 months and 16 years four months respectively. It will be apparent that the clinical state of the adolescent cases described here corresponds fairly closely with the older descriptions of sickle-cell anaemia, confirming our view that outside tropical Africa it has been older children rather than infants who have attracted the attention of physicians.

Manifestations in adult life

The only example of sickle-cell anaemia that we encountered in an adult during the period covered by this report is referred to later (see *Pathology*, p. 417), and there was no opportunity to study this case in life. It is the consensus of opinion in Uganda, as in the Congo (J. and C. Lambotte-Legrand, 1951; Vandepitte and Colaert, 1955) that adults suffering from sickle-cell anaemia are very rare. Nevertheless they do appear from time to time; two of the patients reported by Trowell (1945) were aged 20 and 24 years respectively. It appears that the progressive amelioration noted in older children and adolescents continues in those few who survive, for Dr. G. F. Jacob, working in this unit, has detected mildly anaemic homozygotes in a survey covering several thousand men and women (Jacob, 1957).

Special Features

The haemolytic anaemia. The severity of the anaemia has already been noted; it slowly appeared during the first few months of life, and was usually most

severe in the period six to 24 months, becoming less severe as the child grew older. Anaemia was always present, and it presented all the characteristics of a chronic haemolytic anaemia accompanied by overactivity of the bone-marrow. The level of the haemoglobin fluctuated slightly from month to month, and with the occurrence of intercurrent illnesses; but in the absence of haemolytic episodes, which on the whole were rare, its constancy rather than its fluctuation was remarkable. A critical examination of the stained thick and thin blood films usually offered sufficient data on which a presumptive diagnosis of sickle-cell anaemia could be made. Malaria parasites were usually absent, or if present were scanty and did not appear to explain the severity of the anaemia. It was usually possible to state, on the examination of a thick blood film stained by Field's method, that a haemolytic anaemia was present. This conclusion was founded on the observation of a great increase in nucleated cells, among which normoblasts could often be recognized, and a 'background' crowded with the basophilic envelopes and reticular material of the abnormal erythrocytes (Raper, 1954). The thin blood film revealed target cells in variable numbers; but these were sometimes entirely absent, and were not regarded as of any value in diagnosis. Polychromasia was a marked feature, and reflected a constant reticulocytosis (Table VI) of 3 to 20 per cent.; higher figures were obtained, but a normal reticulocyte count was most exceptional. A constant finding was the presence of large erythrocytes of a diameter from 9 to 12 μ. These were often polychromatic, or appeared obviously leptocytic, with a pale centre and a pessary-like rim. Normoblasts were usually very prominent, and counts up to about 50,000 per c.mm. were recorded. They were reported absent occasionally in adolescent patients, and once in a child of 11 months. Although generally normal in appearance, they sometimes possessed bizarre-shaped or lobed nuclei, and the cytoplasm might show punctate basophilia or Howell–Jolly bodies. Sometimes a few early normoblasts were seen, with polychromatic or even basophilic cytoplasm, the nuclei showing a coarse chromatin pattern. Megaloblasts were never seen. A leucocyte count revealed large numbers of nucleated cells; after correction for the presence of normoblasts, leucocyte counts of 10,000 to 40,000 per c.mm. were usually recorded. Although the proportion of neutrophils was often not increased, juvenile forms were almost always present, and up to 3 per cent. of myelocytes were sometimes recorded.

Sickled cells were often seen in the stained thin film, where they appeared not as crescents, but as elongated, straight or slightly curved, 'cigar' forms. Their prominence varied, doubtless depending to some extent on the exposure of the film to air before it dried, but also depending on the severity of the disease. They were commoner in the older children, and in the more severely anaemic patients, but they might be absent, especially after a haemolytic episode. When numerous, they were regarded as almost diagnostic of sickle-cell anaemia, but it may be noted that we have occasionally seen very scanty sickled cells in the stained blood film of a person having only the sickle-cell trait. Sickling, of course, was always demonstrable in fresh erythrocytes rendered anoxic by the usual methods of moist stasis or bacterial or chemical reduction. Erythrocytes

from a patient suffering from the anaemia sickled rapidly, developed long terminal filaments, and varied much in their appearance; those from sickle-trait subjects sickled more slowly, and developed a blunt leaf-like structure, with small spines along the margins and at the ends. Often these differences allowed a distinction to be made between the trait and the anaemia, but exceptions were encountered, and the shape of the anoxic cells could not be taken as offering data on which a certain diagnosis could be made in every case. With

TABLE VI

Haematological Findings in Sickle-cell Anaemia at Various Ages

Age in years	*Haemoglobin (gm./100 ml.)*	*Erythrocytes (millions/c.mm.)*	*Reticulocytes (%)*	*Normoblasts/c.mm.*	*Mean corpuscular volume (c.μ)*	*Mean corpuscular haemoglobin concentration (%)*	*Leucocytes/c.mm.*	*Serum-bilirubin (mg./100 ml.)*
7/12	5·3	1·87	15	4,600	117	24·1	43,000	0·3
11/12	5·62	1·76	..	7,500	108	29·6	5,800	3·6
1½	3·3	1·12	12	3,200	107	27·2	68,000 (pertussis)	0·5
1½	4·4	1·34	11	20,000	123	27·0	23,000	3·5
2¼	4·0	1·17	16	53,000	124	27·0	23,000	2·6
2¾	8·4	2·41	8	200	105	33·4	10,500	1·5
3	7·35	2·33	12	10,050	100	31·6	32·500	7·0
4	7·86	2·67	..	1,500	97	30·2	23,000	3·6
8	7·6	2·38	20	1,200	94	34·0	23,000	3·0
13	5·9	1·32	12	24,500	138	32·3	12,500	3·0
18	11·1	2·73	7	..	107	36·2	11,200	1·0

this reservation, our experience agrees with that of Neel (1951) and Foy and Kondi (1951). The determination of corpuscular size and haemoglobin-content did not provide much additional information, and the findings in 11 cases in which these values were determined are presented in Table VI. The anaemia was usually macrocytic and orthochromic.

The bone-marrow smear obtained from the iliac crest in young children, and from the sternum in older children, revealed a hyperplastic marrow with very active erythropoiesis. It was studied in 14 cases. Large islands of erythropoietic cells were seen, and these very greatly outnumbered the leucopoietic cells. Normoblasts at all stages of development were plentiful, as were dividing forms. No megaloblasts were seen. Leucopoiesis was active, and megakaryocytes were normal; the other cells normally present in marrow showed no changes. Sickled cells were present in all marrow smears, and drops of marrow blood placed immediately under a cover-slip showed needle-like filaments of haemoglobin in all cases examined, confirming the observations of Vandepitte and Louis (1953).

The persistence of foetal (alkali-resistant) haemoglobin was demonstrated by the technique of Singer, Chernoff, and Singer (1951) in all 14 cases in which it was looked for. In four children in the second six months of life it formed 20 per cent., 11 per cent., 30 per cent., and 7 per cent. respectively of the total haemoglobin. In the second year two cases each gave figures of 19 per cent.; in the

third year the amounts were 8 per cent., 11 per cent., 17 per cent., 19 per cent., and 22 per cent.; and in three children aged eight to 15 years the amounts were 9 per cent., 10 per cent., and 12 per cent. respectively.

The haemolytic crises. Although at all times patients presented evidence of a chronic haemolytic anaemia (Table VI), from time to time episodes of more severe illness occurred, manifesting themselves as fever, malaise, jaundice, and a fall in the haemoglobin level; frequently both the liver and spleen became enlarged and painful. These episodes were of all degrees of severity; in some of them the haemoglobin level fell but slightly, in others the changes were more striking and sudden. For the latter the term 'haemolytic crisis' is considered appropriate as a clinical description. But it must be repeated that these episodes are of all degrees of severity, and unless the case is under careful and continuous scrutiny it is impossible to diagnose the mildest forms. Such observation was seldom possible in our patients, and we were seldom able to observe the mildest episodes, or to follow a severe crisis from its earliest stage.

A fatal haemolytic crisis may occur as early as the third month, and be the earliest clinical manifestation of the disease, as pointed out by J. and C. Lambotte-Legrand (1951); this occurred once in our series (see *Pathology*, p. 416). In the 37 children observed during the first two years of life we encountered 11 severe crises, three of them fatal; in the 35 children aged two to 12 years 14 severe crises were recorded, five of them fatal; none of the six adolescents suffered crises during the period of the survey, but two crises have since occurred among them. A severe haemolytic crisis was a serious illness; it usually started with moderate fever, severe malaise, severe bone and joint pains, vomiting, loose dark stools, and pain over the liver and spleen, both of which organs became tender. Jaundice appeared, and the urine was dark and contained much urobilinogen; the serum-bilirubin rose to 3 to 10 mg. per 100 ml., and continued to give the indirect van den Bergh reaction. In three cases, two of which were fatal, the jaundice deepened, and an immediate positive reaction was given, the serum-bilirubin being 5 to 15 mg. per 100 ml. It was considered that in these cases there was severe parenchymatous disease of the liver, and this belief was confirmed by changes in the serum-globulin and serum-albumin, the thymol turbidity reaction, and the plasma alkaline phosphatase.

By the time the blood was examined there were all the signs of intense erythropoietic activity. Sometimes the haemoglobin concentration continued to fall, but very often the crisis appeared to have passed its peak when the child came under observation. In only one case—the child whose early history is shown in Table III—was a crisis accompanied by signs of hypoplasia of the marrow. This child had been treated with ethyl biscoumacetate ('tromexan'), and it appeared that this unusual feature might be due to the action of the drug. In this case, however, there was no opportunity to examine the marrow, and when death occurred autopsy was not permitted. In all other cases observed while the haemoglobin was falling there was an accompanying reticulocytosis, so that with this exception no hypoplastic crises were observed.

The bones. A characteristic osteopathy appeared in 11 of the 19 children aged

six to 24 months who were observed for long periods in the Child Welfare Clinics. It first appeared as swelling and pain around one of the metacarpal, or less commonly one of the metatarsal bones. The fingers were less commonly affected, usually in the proximal phalanx, though occasionally the middle phalanx was involved. These attacks of osteopathy in the hands and feet might be common and repeated in children from six months to two years of age; they then became far less frequent, and were never seen in a child over six years of age. Osteopathy of the long bones of the limbs was infrequent below one year of age (two cases only); it became more frequent in the early years of childhood (one to six years, 16 cases) and became less severe in later childhood. Whichever bone was attacked, a fairly constant sequence of events was noted. In early childhood severe pain and fever occurred, to be followed within a day or two by swelling, heat, and oedema over the affected bone, which thus resembled one affected by an acute infective osteomyelitis. Then, without treatment, the inflammatory signs usually slowly subsided; in most cases only moderate residual thickening and tenderness could be detected after 14 days, and pain had almost disappeared; most patients displayed no clinical signs at the end of 30 days, but in a few some thickening persisted, and a minority suffered a relapse of pain and swelling. Unless another episode of osteopathy occurred, clinical examination suggested that resolution was complete in most cases at the end of 30 to 50 days.

Radiological examination of the part usually revealed no bony abnormality in the first seven to 10 days; then a fine increase in the periosteal shadows occurred, the shaft became blurred at its margins, especially on the outer surface, and a variable degree of rarefaction might be seen within the medulla. These changes were most evident in the metacarpal and metatarsal bones. In one case a pathological fracture of the first metacarpal occurred, in another case abscess formation occurred in a metacarpal bone, and from the pus *Salmonella typhimurium* was isolated. In older children the long bones of the limbs showed varying degrees of periosteal reaction as an almost constant feature, as one attack of osteopathy succeeded another. Irregularities in the cortex or medulla were seldom conspicuous, and often absent; the peripheral long bones (radius, ulna, tibia, and fibula) appeared to be more frequently attacked than the proximal bones. One case of spontaneous transverse fracture of the femur was seen in a young child after the close of the survey. One case of chronic hip disease resembling osteochondritis juvenilis (Perthe's disease) was detected in one of the adolescent boys, who at the age of 15 was admitted to the surgical wards of Mulago Hospital. Radiologically there was necrosis of the head of the femur and the adjacent acetabular region. Treatment was conservative, and two years later the patient was walking with only a slight limp. In older children, and especially those seen in adolescence, it was usually possible to detect some coarsening of the trabeculae and thinning of the cortex of many of the long bones; lines of arrested growth were commonly seen. In no case was it possible to demonstrate areas of increased cortical translucency. The long bones of adolescents corresponded in form with the thin, tapering limbs, and

there was retardation of bone growth and bone age. These changes will be the subject of a separate communication; the selection of cases from different tribal groups, and the absence of data regarding normal standards, render interpretation difficult.

Bossing of the skull appeared to have a different aetiology. It was not noted in any child below 12 months, but then became increasingly frequent, so that obvious radiological abnormality was present in half the patients aged one to eight years, and in two out of six adolescent patients. In most of these cases the bossing could be seen clinically (Plate 41, Figs. 1 and 2), and was most marked over the central portions of the frontal, temporal, and occipital bones, a shallow sulcus running along the lines of the sutures. Radiological examination revealed a progressive increase of the cancellous diploë and thinning of the cortex, imparting, in advanced cases, a 'hair-on-end' appearance to the radiograph. The outer table was thinned at an early stage; there was no change in the inner table. Comparable changes, but less marked, consisting presumably in an increase of the erythropoietic marrow and a decrease of the thickness of the cancellous network and a decrease in the cortex, were detected in two cases in the vertebrae, and in 10 cases in the limb bones, of the older children and adolescents. This bossing of the skull and increase in the medullary cavity of the long bones was painless, and persisted at least for several years—although it might eventually slowly disappear during later childhood and adolescence—and bones thus affected were seldom the site of an acute osteopathic swelling. Post-mortem material suggests that these changes reflect an increased vascularity of an overactive and enlarged erythropoietic marrow; autopsy data concerning the acute osteopathy are completely lacking. It has been suggested that the latter form of osteopathy is due to localized vascular stasis, and possibly secondary thrombosis of vessels and necrosis of small areas of bone, with subsequent slow absorption, and eventually a return to the normal bone structure; occasionally there might be a superimposed infection. If an acute osteopathy occurred near a joint, a small effusion sometimes occurred, and the inflammatory reaction might involve the surrounding soft tissues. In adolescents these changes often appeared to be limited to a joint or joints, which thus showed all the signs of an acute non-suppurative inflammation, resembling the changes found in acute rheumatism. In these cases no abnormality of the bones could be detected radiologically.

Other complications. Cardiac enlargement was detected in 18 of the 24 patients examined radiologically. It was present in all those aged four years and upwards (16 cases). If fever, limb and joint pains, leucocytosis, and splenomegaly were present, the case might resemble one of rheumatic carditis. But the softness of the systolic murmurs of sickle-cell anaemia, the anaemia itself, the jaundice, and the character of the osteopathy usually offered clear points of distinction, as did the failure to respond to salicylates. Chronic cardiac failure, accompanied by and presumably due to the severe anaemia, occured in three patients; acute circulatory failure was a prominent feature in seven patients who had acute haemolytic crises. Both of these types of cardiovascular

disorder might be accompanied by much pain over the enlarged liver, but this occurrence, in our opinion, should not be called an 'abdominal crisis'. A different type of upper abdominal pain occurred in three of the older children. The attack showed itself as pain in the upper abdomen, severe vomiting, and low fever; the liver and spleen were usually enlarged and tender. In no case was there evidence of gall-stones or cholecystitis, and though pigment stones have been detected in cases of sickle-cell anaemia in previous years, they are but rarely seen in Uganda. These attacks are unexplained; they may represent vascular accidents in the hepatic or mesenteric vessels. They may be called abdominal crises, but none were fatal, and it is notable that they were observed only in the older children.

No case of a vascular accident in the central nervous system was encountered in the present series, and such accidents appear to be very rare in sickle-cell anaemia in Uganda. But one of the adolescents recorded here had been admitted six years previously to another hospital, where he was comatose for three days, had a normal cerebrospinal fluid, and subsequently recovered completely. Another boy of six years (not included in this series) suddenly developed convulsions and a left hemiplegia. He was admitted to Mulago Hospital; the cerebrospinal fluid was normal, and no cause apart from sickle-cell anaemia was detected. There was little recovery when he was discharged two weeks later. One child had mental deficiency and fits, but there was nothing to suggest that these disorders were connected with the anaemia (autopsy no. 4, p. 416). In only one case was there evidence of thrombophlebitis of a large vessel; one child, dying in a haemolytic crisis, had a femoral thrombosis. Tortuous retinal vessels were observed in all children of 12 years of age or over (six cases); below that age no special search was made for this sign, because of difficulty in securing co-operation. No leg ulcers were present in any of our patients.

Associated malaria was occasionally present, and was always mild in character. Among 21 children attending for many months at Child Welfare Clinics, only six were observed to contract an attack of *falciparum* malaria; this infection was found in three hospital patients, and another two showed *P. malariae*, and one a *P. ovale* infection. No case of intense malarial infection, defined arbitrarily as one in which more than one per cent. of the erythrocytes were parasitized, was found in this series.

Pathology

Of the seven deaths observed in hospital in the present series it was possible to secure an autopsy in only two cases (Nos. 2 and 3, below). The point will be made subsequently that the lack of distinctive macroscopic changes at autopsy might allow the diagnosis to be missed unless the disease had been recognized during life. For these reasons, particulars of all cases of proved sickle-cell anaemia examined *post mortem* by one of us (A. B. R.) in the period 1950–5 are now given. Of the two adults seen *post mortem* who had a haemolytic anaemia

and sickling, one has been excluded; he was a young man of 21 years, whose father (the only parent available) failed to show sickling. Five autopsies are now described, arranged in order of the age of the subjects.

1. *An infant of three months.* The age of this Ganda male baby was accurately known, as he was born in prison. Death occurred without any reported illness, and autopsy was performed five and a half hours after death. The weight was 6·35 kg. There was extreme anaemia, and blood films prepared at autopsy showed the fully developed picture of sickle-cell anaemia; there was no evidence of malaria, and electrophoresis of the haemoglobin showed a band in the position of haemoglobin-S, with trailing ascribed to the presence of some foetal haemoglobin.

The spleen weighed 190 gm., being about four times the normal size. It was very firm and turgid, of a deep maroon colour. The follicles were visible as dead-white dots, with no special congestion in their vicinity. Microscopically there were no perifollicular 'lakes' of blood, but the whole pulp was packed with sickled cells. There was no fibrosis or siderosis, and staining for iron gave a negative result. There was no bossing of the skull, and there were no enlarged or erythropoietic lymph-glands. The liver was of normal size, rather pale; it showed microscopically active erythrophagocytosis by the Kupffer cells, which contained fine dots of iron; there was no distension of the sinusoids, but erythropoietic cells were present in small numbers. There was faint iron-staining in the proximal tubules in the kidneys. Other organs showed capillary collections of sickled cells, but no other significant lesions.

2. *An infant of 10 months.* In this Luo female child the diagnosis had been established haematologically and electrophoretically at the age of six months. Death occurred from pneumonia following malnutrition and thrush. Two blood transfusions had been given shortly before death.

The spleen (25 gm.) was of normal size and appearance. Histologically it showed a pulp generally empty of blood, except around the rather atrophic follicles, where there were narrow zones of pooled sickled cells. There was no sidero-fibrosis, and only a faint iron reaction in some of the large macrophages. The liver showed no congestion, no evidence of malaria, no iron-staining reaction, and no erythropoiesis. The skull showed a few patches of parietal thickening, with brown liver-like discoloration; the ribs and the bones of the hands were normal. The kidneys were normal, showing faint traces of iron in the convoluted tubules. There were small erythropoietic foci in the aortic lymph-glands.

3. *A child of two years.* A Ganda male child died about the 11th day of an attack of typhoid fever, confirmed by blood culture; the diagnosis of sickle-cell anaemia had been made haematologically and by electrophoresis.

The appearance of the spleen, weighing 20 gm., was modified by typhoid; but it showed no sidero-fibrosis, and the amount of iron-staining material was very small. The liver showed oedema of the sinusoids, distension of the capillaries with sickled cells, and many small areas of necrosis; these did not resemble the focal necroses of typhoid, being devoid of phagocytic cells and packed with sickled erythrocytes. In the skull the parietal eminences were just visibly increased in size, without definite bossing. There was a faint reaction for iron in the kidney tubules.

4. *A child of five years.* This Tesot female child died of a primary tuberculous bronchopneumonia, one year after a diagnosis of sickle-cell anaemia had been made after full investigation. She was a mentally retarded epileptic, with a

history of a head injury at two years of age. At autopsy there was no evidence of past injury to the skin or bone of the skull, but the dura, arachnoid, and brain were adherent in the left parietal region, and showed some yellow staining. The appearance of the bones of the vault of the skull was within normal range.

The spleen (150 gm.) was about normal in size, but more globular than usual; it was dense and rubbery in consistency. The surface was uneven, and on section this could be seen to be caused by the alternation of swollen purple pulp and fine bands of early fibrosis. No follicles were visible, and microscopically the congested pulp was intersected by an increased number of trabeculae, of which few exceeded 0·1 mm. in thickness; some of these contained very small ferrous incrustations. Lymph-glands in the thorax and upper abdomen were large and brown, and showed a deposit of ferrous material in the reticulum of the medulla. The liver (760 gm.) showed only distension of the sinusoids with sickled cells. In the kidneys the tubules gave a strongly positive iron reaction, but there were no anatomical lesions.

5. *An adult woman.* This Ganda patient had given her age as 36, but her appearance was that of a woman of about 25 years. She had given birth normally to a female child after about seven months' gestation, after which she was noticed to be feverish and jaundiced, and she collapsed and died suddenly. There had been no investigation before death, but her blood at autopsy was characteristic of sickle-cell anaemia, the cells assumed long needle-like shapes, and 18 per cent. of the haemoglobin was resistant to alkali denaturation. Unfortunately no electrophoretic analysis was made, this being the one exception in the present series, but the diagnosis was considered reasonably certain.

She was a slim young woman, with tapering legs and arms. There was jaundice, and oedema of the ankles, and the blood was watery and jaundiced. The skull was enlarged, of 'hot-cross-bun' shape; the parietal, and more notably the frontal, bones were thickly bossed, with deep red-brown diploë, the surface being rough and red. The petrous part of the temporal bones was thicker and softer than normal, while the squamous part, and the occipital bone, showed patches where the diploë was absent. The spleen (40 gm.) was of the size and shape of an adult tongue, the capsule being slightly thickened and wrinkled. Its pulp was dry and firm, intersected by numerous fine yellow trabeculae; there were no infarcts. Microscopically there was gross sidero-fibrosis. There was a considerable mass of enlarged lymph-glands in the upper abdomen, soft and brown, and showing a positive reaction for iron. In the liver the sinusoids were distended with long sickled cells, normoblasts, and Kupffer cells swollen to an enormous size—some full of erythrocytes, others loaded with haemosiderin—there were a few small foci of necrosis and resultant fibrosis. The kidneys showed every glomerulus stuffed with sickled cells, and heavy iron-staining of the convoluted tubules. There were scattered foci of sclerosis, involving two or three glomeruli and the intervening tissue. Other organs, including the heart, lungs, adrenals, pancreas, brain, and pituitary, showed no notable lesion.

Comment. The most noteworthy fact about these observations is that the development of visible changes in the spleen, lymph-glands, and flat bones lags well behind the appearance of the anaemia. The spleen is the organ most constantly affected at an early stage, but its congested state is in no way diagnostic, and it is only as childhood advances that the characteristic sidero-fibrosis appears. Similarly, visible extramedullary erythropoiesis is of slow development. At an early stage of the disease the presence of iron-containing deposits

may not be demonstrable either at autopsy or in sections of the organs, and indeed it has been noticed at Kampala that the convoluted tubules of the kidney in malaria may carry quantities of iron far in excess of those present in small children with sickle-cell anaemia. We are satisfied that even at a carefully conducted autopsy it is possible to miss entirely, or to misinterpret, the scanty morbid changes when an infant dies of sickle-cell anaemia. At about the age of five years sidero-fibrosis of the spleen may appear, and thereafter the morbid changes that accompany any chronic haemolytic anaemia accumulate, so that, paradoxically, the less lethal the anaemia the more evident are its results to the pathologist.

Although there are many descriptions of the pathology of sickle-cell anaemia, notably in the medical literature of America (Steinberg, 1930; Diggs and Ching, 1934), it is probable that those appearing before 1951 contained examples of the variants as well as of the 'pure' disease. Edington (1955), however, in giving a comprehensive account of the pathology in West Africa, after it had been established that haemoglobin-C was common there, recognized that since there had been no haemoglobin analysis in his cases they must have included 'conditions in which the sickle-cell haemoglobin is in combination with the abnormal haemoglobins'. Edington's results in the Gold Coast are of great interest. He distinguished two types of finding at autopsy: in 12 cases a small siderotic spleen was found, but in 92 cases the spleen was large and congested. No small scarred spleens were found below the age of five years, as in our small series, but on the other hand he found large congested spleens in patients who died in 'crisis' up to the fifth decade of life. Such large spleens had also been found in America (Diggs and Ching, 1934; Tomlinson, 1945). But we have never met this combination of what appeared to be a sickling crisis with a large spleen in an adult. The implication is that this type of spleen is not a feature of 'pure' sickle-cell anaemia, in which the march of the disease is so rapid that survivors are few, and in these few the sclerosis of the spleen is well advanced.

Treatment and Prevention

Little can be done to influence directly the course of the disease, or to lessen the severity of the haemolytic crises. It is probable that if more attention could be given to the nutrition of the child, especially after weaning and during early childhood, while at the same time any departures from normal health received prompt attention, many lives could be prolonged. It is noteworthy that all patients who survived to adolescence came from the higher social groups. Blood transfusions are of great benefit, and were given to 16 patients in the present series; three children received two or more transfusions. The benefit of course is only temporary, but transfusion probably prevented anoxic death in several cases. The scarcity of blood donors in Uganda prevented their employment as frequently as might be desired. We have not used splenectomy or corticotrophin because of the poor results reported (Dacie, 1954). Hopes were raised by the discovery (Griffiths, 1955) that ethyl biscoumacetate ('tromexan'),

in doses that reduced the prothrombin time, inhibited sickling *in vivo*. We considered this drug unsafe in prolonged treatment of African children, but were prepared to try it in a severe crisis. As recorded above, the attempt in one case was unsuccessful; sickling was abolished or much reduced, yet the child died with signs of marrow failure. Nevertheless, the knowledge that the sickling process can be prevented by chemical action may provide the basis for safer therapy in the future.

When a case of sickle-cell anaemia had been detected, and both parents had been proved to carry the sickling gene, no advice was given concerning future pregnancies. It is doubtful if any advice would be accepted, and the chance of any future pregnancy resulting in a homozygous child is only one in four. The chances are even that the child will be heterozygous, and so survive the dangers of malaria better than a normal child. As far as can be foreseen, the incidence of sickling will decrease slowly as public-health measures decrease the incidence of malaria in tropical Africa; such a change is supposed to have taken place in the Negro population of America (Allison, 1954–5).

Discussion

The picture presented here is that of a severe disease, appearing first as a rather mild disorder during, or soon after, the third month of life. From the age of six months, however, the evolution of the disease is rapid; the anaemia soon attains a moderate severity, and incidents such as fever, pain and swelling of the hands or feet, jaundice, and enlargement of the spleen and liver occur, and may mimic malaria. In particular, the frequency of osteopathy of the bones of the hands and feet is worthy of note, since in African children it occurs in almost no other disease save congenital syphilis, and is recurrent, in our experience, only in sickle-cell anaemia. It is almost confined to the first two years of life, after which age the long limb bones are more commonly affected. Although fully described by J. and C. Lambotte-Legrand (1951), this early osteopathy is barely mentioned in American reports; but in fact it is the most distinctive clinical sign at the onset of the disease. From time to time, but at infrequent intervals, there are severe haemolytic episodes that increase the anaemia and are often fatal, so that many deaths take place between the ages of six and 24 months. Thus J. and C. Lambotte-Legrand (1955), in their series of 300 cases of sickle-cell anaemia in the Belgian Congo, found that 10 children died before six months of age, and 62 died between the sixth and 24th month. After three years of age deaths were less frequent, but out of the total series 150 patients died after periods of observation of up to five years. In the present series of 59 clinical cases there were 11 known deaths, but only a minority of patients could be followed for periods over a year. Six of the 11 deaths occurred under 24 months of age; in addition three out of five autopsies were performed on infants in the first two years of life. The apparent severity of the disease in early childhood is perhaps increased in African infants because at the same time so many of them experience underfeeding and protein malnutrition, and are subject

to untreated intercurrent infections, especially respiratory disease; many come for treatment late, and blood transfusion is available to very few.

In the present series there were only six cases in adolescence (12 to 18 years), and no cases in adult life. Drs. J. and C. Lambotte-Legrand, being paediatricians, were possibly not in a position to examine many adults, but Vandepitte (1954), also working in the Belgian Congo, has recorded 261 cases of sickle-cell anaemia, only 10 of which were in patients over 10 years of age, and only one in an adult. Although there is evidence in these studies from the Belgian Congo, as in the present series, that the disease tends to become less severe, and haemolytic crises less frequent, as the children grow older, yet the proportion who survive to adult life and can reproduce is probably very small. If patients first present themselves during adolescence or later, they may maintain that they were well during early childhood. This may be because episodes of illness in infancy have been forgotten, or because they were very mild and were confused with malaria, and therefore regarded as of no consequence, or because there were no such episodes and the anaemia was only mild. A fourth possibility is that even anaemia was absent until later in life, but this appears improbable, because we have not encountered or heard of a child proved to be homozygous for the sickling gene who did not exhibit signs of sickle-cell anaemia. Our data, though scanty, support the established view that many of the adolescents develop a characteristic physique, with long thin limbs and an asthenic build. In America this habitus was found by Smith and Conley (1954) to be more usual in 'pure' sickle-cell anaemia than in haemoglobin-C:sickle-cell disease. Hypogonadism was thought to be present in some of the adolescents in our series; this might decrease fertility if the patient survived to adult life, but precise information on this point is lacking.

The present study reveals many differences between the pattern of the disease as seen in Central Africa and that recorded in West Africa and America. The most important differences lie in its early age of onset, rapid rate of evolution, and high mortality in infancy in Central Africa. In Wintrobe's (1951) textbook the early onset is qualified by the remark: 'It is noteworthy that there is a record of but six cases of sickle-cell anaemia before six months of age, and only six more in the succeeding age period six months to one year'; and Diggs and Ching (1934) give the expectation of life as 'less than 30 years'. Many of Edington's (1955) patients in the Gold Coast were adults. Our experience described above is quite different, and agrees with that of the Belgian workers. The difference in mortality may be connected with differences in general infantile mortality in the various countries, but this cannot be the whole explanation, nor does it explain the early onset and rapid progress of our cases. It is notable that in America the average age at onset in the 37 patients of Scott, Banks, Jenkins, and Crawford (1951) was 3·5 years, only 10 giving any history of an onset before the age of one year; moreover, though pain in the extremities was the commonest symptom, there is no mention of the bony swellings that are so characteristic a feature in African children. It may be that the absence of other haemoglobin variants in Central Africa accounts for much of the difference, and it remains to be seen

whether careful surveys among American Negro infants will reveal much closer agreement with the pattern of disease in Africa when the 'pure' disease in the two continents is considered. The very severity of the disease in our patients probably explains the absence of many of the other complications often described, for these usually appear in adolescence or later. None of our patients showed leg ulcers, neurological manifestations were infrequent, and gall-stones and renal failure were absent. Only three complained of upper abdominal pain possibly due to the disease, only one showed rarefaction of the cortex of a long bone, and other forms of vascular accident or thrombosis were notably rare.

We wish to thank Dr. G. F. Jacob for her help, especially in the electrophoretic studies, determination of alkali-resistant haemoglobin, and control of 'tromexan' therapy; Dr. G. M. Davies for assistance in radiology; Dr. M. D. Thompson for details of one of the cases; and Dr. L. K. Musoke for help in the collection of data.

Summary

1. An account is given of the course and clinical features of sickle-cell anaemia in 59 children in Uganda. All were proved to be homozygous for the sickling gene.

2. The apparent incidence of the disease is in agreement with the theory that it develops in children who are homozygous for the gene, and the magnitude of the paediatric problem in Africa is noted.

3. The anaemia appears in the first few months of life, runs a severe course, and causes much mortality in early childhood, but becomes rather less severe in later childhood and adolescence. Adult sufferers from the disease are very rare in Uganda.

4. Details are given of five autopsies; one was in an adult patient.

5. The present series shows differences from the classical descriptions of the disease, notably in the early age of onset, the rapid progress of the disease in early infancy, the frequency of characteristic bony swellings of the hands and feet, the low survival rate, and the paucity of thrombotic incidents and leg ulcers. Reasons for these differences are discussed.

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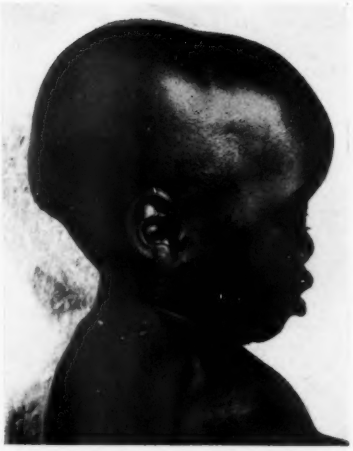

FIG. 1. Bossing of shaved head and grooves along lines of sutures in a child of two years

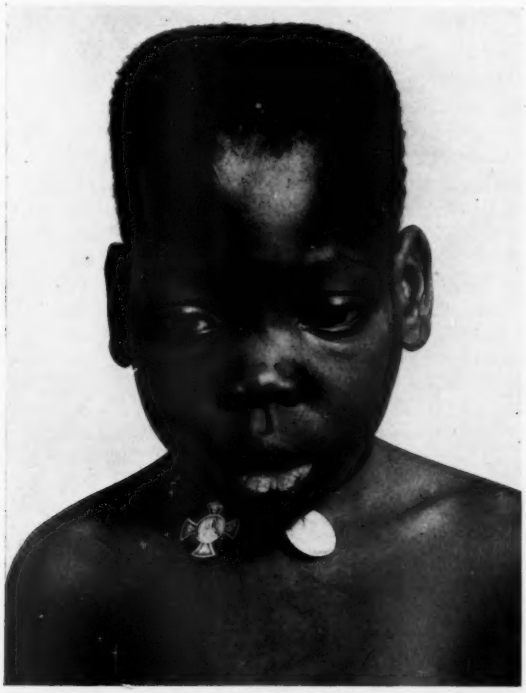

FIG. 2. Bossing of head and longitudinal groove in a boy of eight years

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POLYURIA IN HYPERPARATHYROIDISM[1]

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Polyuria is a characteristic symptom of hyperparathyroidism. Frequently the output of urine is so great, and its concentration so low, that diabetes insipidus is suspected (Gutman, Swenson, and Parsons, 1934; Alexander, Pemberton, Kepler, and Broders, 1944), especially when there are no calculi or radiological evidence of renal calcification (Snapper, 1952). We have investigated the problem of the polyuria in two patients with hyperparathyroidism, in whom one of the most prominent symptoms was the excretion of large volumes of urine hypotonic to plasma.

Case 1. T. E. K., aged 37, an engine driver in a coal mine, was admitted on April 10, 1955. For two years he had been thirsty and passing large amounts of urine; he was continually drinking water, and in addition consumed daily a half to one litre of milk. He had lost 20 kg. of weight, and was increasingly tired and constipated; he occasionally vomited; for one year he had had severe frontal headaches. He looked ill and severely dehydrated; his mouth was so dry that he could hardly speak. His temperature was normal, pulse-rate 80 to 100, blood-pressure 160/100 to 160/120, weight 44·9 kg., and height 171 cm. His heart was not enlarged, and his optic fundi were normal. There was a small nodule, difficult to feel, under the origin of the right sternomastoid. The blood-urea on admission was 70 mg. per 100 ml., and fell to 24 mg. per 100 ml. as the dehydration was corrected; the plasma contained sodium 140 mEq., potassium 4·7 mEq., and chloride 110 mEq. per litre; serum-calcium ranged from 15·8 to 17·0 mg., and serum-phosphorus from 2·1 to 3·3 mg. per 100 ml., and the serum alkaline phosphatase was 9·0 King-Armstrong units per 100 ml. Plasma-proteins were 6·9 gm. per 100 ml., with a normal electrophoretic distribution. The urine usually contained a trace of protein; its mean daily volume during 10 days was 5·2 litres, with a range of 3·7 to 6·0 litres; it was dilute, with a specific gravity between 1,002 and 1,004, but always formed a white precipitate on standing. On an ordinary diet the daily excretion of calcium was about 1 gm., and after five days on a diet containing only 120 mg. of calcium it was still 540 mg. Other observations on renal function are described below. X-rays of the skeleton, including the skull and hands, and of the kidneys, including renal tomograms, were normal.

On May 18 Professor Lambert Rogers removed a parathyroid adenoma about 2 cm. in diameter, composed mostly of 'chief' cells, with some oxyntic and vacuolated cells (Dr. J. H. Whitely). The patient lost little blood, and his blood-pressure did not fall, but the large excretion of urine stopped, and in the next 24 hours he passed only 220 ml. (compare Snapper, 1943; Black, 1953),

[1] Received November 24, 1956.

much of which must have been formed before the adenoma was removed. The specific gravity of this urine was 1,011. The blood-urea on the day after operation was 61 mg. per 100 ml., and 10 days later 34 mg. per 100 ml. The diminution of serum-calcium, urinary calcium excretion, and urinary volume induced by the operation are illustrated in Fig. 1. After the first day the daily urine volume ranged from 1·4 to 2·4 litres. From the time of operation the patient lost his thirst, and five days later he had gained 5·2 kg. in weight. Three to four weeks after operation he had transient oedema of the ankles (compare Moulonguet and Lièvre, 1938). Three months later he had returned to work and regained his normal weight of 70 kg. The blood-pressure was 165/120, and the urine was free of protein. Details of renal function after operation are given below.

Glomerular function and effective renal plasma-flow. Inulin clearances were used to measure glomerular filtration rate (inulin estimated by the method of Roe, Epstein, and Goldstein, 1949), and *p*-aminohippurate (PAH) clearances to measure effective renal plasma-flow (method of Brun, 1951). The clearances before operation were low (inulin clearance 52 ml. and PAH clearance 228 ml. per minute); at this time the blood-urea was 24 mg. per 100 ml. Five days after operation these values had not changed (inulin clearance 51 ml., PAH clearance 207 ml. per minute), but six weeks after the operation the inulin clearance had increased to 80 ml. and the PAH clearance to 337 ml. per minute.

Tubular function. 1. *Hydrogen ion excretion.* Before operation 93 mEq. of ammonium chloride were given daily for five days, but the pH of the urine never fell below 6·7, and after removal of the CO_2 there was no titratable acidity; excretion of sodium, however, increased from about 100 mEq. to 200 mEq. per day, and the excretion of ammonia, which was not impaired, increased from 99 mEq. to 166 mEq. daily. Six weeks after operation the same daily dose of ammonium chloride reduced the pH of the urine to 5·9, and the titratable acidity of the urine rose to 33 mEq. per day. The ammonia was not measured.

2. T_mPAH. Before operation the maximum capacity of the tubules to excrete PAH was considerably decreased (18·6 mg. per minute). It was not measured again after operation.

3. *Maximum concentrating capacity.* Before operation, when the patient was deprived of water for 10 hours—the longest period his thirst would allow—the specific gravity of the urine rose only to 1,007, and the rate of urine flow did not fall below 1·24 ml. per minute. When the test was repeated a few days later, but with the addition of pitressin (three doses of 20 units intramuscularly at four-hourly intervals), the specific gravity of the urine still did not rise above 1,008, and the rate of urine flow did not fall below 1·3 ml. per minute. On a third occasion, when the patient's fluid intake was not being restricted and the urine flow was steady at 4·6 ml. per minute, an infusion of 320 ml. of 2·5 per cent. sodium chloride administered in 20 minutes (Hickey and Hare, 1944) reduced the urine flow only to 3·8 ml. per minute. If it is assumed that the neurohypophysis was normal, this steadiness of the urine flow implies that the kidneys' response to endogenous antidiuretic hormone was no greater than to injected pitressin. One week after operation the capacity to concentrate had improved and, when the patient was deprived of fluid for 13 hours, the specific gravity rose to 1,014, and the urine flow fell to 0·46 ml. per minute, although the clearances of inulin and PAH had not yet changed. Six weeks after operation, when the patient was deprived of fluid for 21 hours, the specific gravity rose to 1,020, and the urine flow fell to 0·30 ml. per minute.

Case 2. Miss D. G., aged 53, a telephonist, was admitted on November 16, 1955. For 10 years she had been abnormally thirsty, and had had nocturia;

during this time she had also felt increasingly tired. Early in September these symptoms had become worse, and at the end of October she had had to stop work. For two years she had had intermittent heartburn, relieved by alkalis. Nine days before admission she had begun to vomit two to seven times a day, and for three days she had been constipated. She was a thin, ill woman, with a dirty-yellow pigmentation of the skin, and pale mucosae. She was co-operative, and at first answered questions, and was able to move with some difficulty.

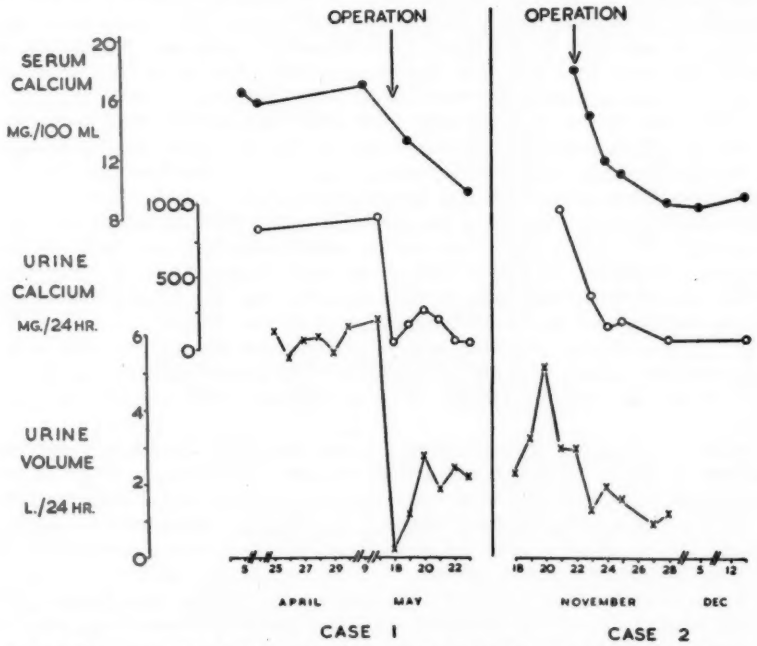

FIG. 1. Serum-calcium, daily urinary excretion of calcium, and urine volume, before and after operation.

After two days, though conscious, she hardly reacted when spoken to. The tongue was dry, the turgor of the skin diminished, and the eyes sunken. Her temperature was normal, pulse-rate 100, blood-pressure 120/85, and jugular venous pressure normal. She weighed 43·5 kg. The blood-urea was 106 mg. per 100 ml.; the plasma contained sodium 140 mEq., potassium 3·3 mEq., chloride 90 mEq., and bicarbonate 23 mEq. per litre, and 6·8 gm. of proteins (albumin 3·9 gm., globulin 2·9 gm.) per 100 ml. The haemoglobin was 11·8 gm. per 100 ml. of blood, and leucocytes 8,400 per c.mm. The urine had a trace of protein, and considering the evidence of dehydration its volume was very large (2,075 ml. and 2,580 ml. on the first two days after admission); it formed a white precipitate on standing, although the specific gravity was low, ranging between 1,002 and 1,008. With treatment during the next few days the urine volume became even greater, and the blood-urea level fell to 66 mg. per 100 ml. Because the urine continued to be hypotonic, the serum-calcium was estimated on November 21; it was 22 mg. per/100 ml. On the following day the calcium was 17·8 mg., the phosphorus 5·2 mg., and the alkaline phosphatase 4·5 units per 100 ml. of serum; the urinary excretion of calcium was 950 mg. in 24 hours (21–22.11.55). An

electrocardiogram showed a diminished QT interval. Radiologically the bones of the hands appeared decalcified; there were periosteal erosions of the phalanges characteristic of hyperparathyroidism, and one cyst in a metacarpal bone; X-rays also showed calcium in both kidneys. There were multiple minute, white, punctate opacities in the deep layers of the cornea, more numerous at the periphery. Other observations on renal function are given below.

On November 22 Professor J. B. Kinmonth removed two parathyroid adenomata, measuring 6×3 cm. and $3{\cdot}5 \times 2{\cdot}5$ cm. The cells in both tumours were mainly 'chief cells', though a minority were 'clear cells'; there were only a few oxyntic cells (Dr. J. Pinniger). The day after operation the patient was cheerful and alert, and her thirst had disappeared. The urine volume, serum-calcium, and urinary calcium excretion quickly returned to normal (see Fig. 1). Two days after operation there was a transient increase of blood-urea to 158 mg. per 100 ml.; a week later it was 46 mg. per 100 ml. Seven days after operation she had tetany, which was treated with calcium lactate and calciferol. Five weeks after operation her legs became oedematous, and her jugular venous pressure rose by 3 cm.; the blood-pressure was 180/90, and an electrocardiogram was normal. She left hospital nine weeks after admission, with some residual oedema of the ankles. In March 1956 the patient returned to work. In September 1956 she felt well; there was no oedema of the legs, the jugular venous pressure was normal, and the blood-pressure 180/110; her weight had increased by 15 kg. The blood-urea, however, was still 53 mg. per 100 ml., and the haemoglobin remained about 11·6 gm. per 100 ml. The serum-calcium was between 9 and 10 mg. per 100 ml. Details of renal function after operation are given below.

Glomerular function. Before operation the creatinine clearance (creatinine measured by the method of Bonsnes and Taussky, 1945) from a single 24-hour urine collection, and from shorter collections by catheter, varied between 10 ml. and 15 ml. per minute. After operation the 24-hour clearance of creatinine increased only gradually; after six weeks it was still only 39 ml. per minute, and after nine months 42 ml. per minute.

Tubular function. Maximum concentrating capacity. Two days before operation the patient was given 100 milli-units of pitressin intravenously, followed by a continuous infusion of 5 milli-units per minute for about two hours; after 60 minutes 450 ml. of 25 per cent. mannitol were given through another vein at the rate of 7·5 ml. per minute. This hypertonic infusion rapidly increases the output of solute; it also stimulates the neurohypophysis to liberate antidiuretic hormone (de Wardener and McSwiney, 1951). The kidneys were thus exposed not only to injected pitressin but also (if the neurohypophysis was normal) to increased concentrations of circulating antidiuretic hormone. The urine was collected by catheter at intervals of five to 15 minutes and the osmolar concentration calculated from freezing-point determinations (de Wardener and del Greco, 1955). Osmolar clearance $\left(\frac{Uosm. \times V}{Posm.}\right)$ was calculated by dividing the solute output in osmoles ($Uosm. \times V$) by the osmolar concentration of the plasma ($Posm.$); this clearance is the volume in which the solutes of the urine would be excreted at the osmotic concentration of the plasma. Free water excretion is the difference between the actual volume of the urine and the osmolar clearance; it is therefore positive when the urine flow is greater than the osmotic clearance, and negative when it is smaller (Wesson and Anslow, 1948).

The results are given in the Table, and illustrated in Fig. 2. The injected pitressin raised the osmolarity of the urine from 125 to only 259 mOsmol. per litre, a concentration 46 mOsmol. per litre below the osmolarity of the plasma.

The infusion of 25 per cent. mannitol raised the plasma osmolarity, the solute output, and the urine flow. At the height of the diuresis the urine flow was 63 per cent. of the creatinine clearance, and the urine, which was already hypotonic at the beginning, became even more dilute, with an increase in free water excretion from +0·46 ml. to +2·6 ml. per minute.

Renal Function in Case 2 Before and After Operation

Urine specimen	*Time (min.)*	*Urine flow (ml./min.)*	*Urine osmolarity (mOsmol./l.)*	*Plasma osmolarity (mOsmol./l.)*	*Solute excretion μOsmol./min.)*	*Free water excretion (ml./min.)*	*Creatinine clearance (ml./min.)*
Before operation:							
1	0–15	3·5	125	305	400	+1·88	12
Intravenous pitressin 100 m. units followed by 5 m. units/min.							
2	15–30	1·53	213	..	326	+0·46	11
3	30–45	1·13	225	..	254	+0·29	12
4	45–60	1·2	255	..	306	+0·20	15
5	60–75	1·4	259	305	364	+0·21	14
Intravenous 25 per cent. mannitol 7·5 ml./min.							
6	75–90	2·4	240	..	575	+0·54	18
7	90–105	6·5	232	318	1,520	+1·75	22
8	105–120	10·8	257	..	2,750	+2·55	20
9	120–135	12·7	260	327	3,300	+2·6	20
After operation:							
1	0–21	1·80	408	307	734	−0·85	38
Intravenous pitressin 100 m. units followed by 5 m. units/min.							
2	21–38	0·94	389	..	366	−0·12	36
3	38–54	1·56	389	..	606	−0·41	54
Intravenous 25 per cent. mannitol 7·5 ml./min.							
4	54–72	1·39	395	..	549	−0·38	48
5	72–80	1·44	402	313	578	−0·42	50
6	80–90	4·5	376	..	1,690	−0·92	105
7	0–95	5·2	366	..	1,865	−0·67	78
8	95–100	9·4	357	322	3,360	−1·00	81

Twelve days after operation pitressin and mannitol were again given in the same way (Table and Fig. 2). The highest urine osmolarity was now 402 mOsmol. per litre, that is 89 mOsmol. per litre greater than that of the plasma. The infusion of 25 per cent. mannitol raised the plasma osmolarity, the solute output, and the urine flow over a similar range to that obtained before operation, but the osmolar concentration of the urine, though it decreased, remained above that of plasma, and throughout the diuresis was greater than the concentrations found before operation; the calculated excretion of free water, which was negative, fell from −0·41 to −1·0 ml. per minute. Nineteen days after operation 36 hours' deprivation of fluid raised the osmolarity of the urine to 615 mOsmol. per litre; during the last eight hours the urine flow was 0·48 ml. per minute. Twenty-five days after operation an intramuscular injection of five units of pitressin tannate in oil raised the osmolarity to 552 mOsmol. per litre.

Renal structure. Thirty-eight days after operation a biopsy of the kidney was obtained with a needle. Some glomeruli appeared normal, others showed a wide band of periglomerular fibrosis, and yet others were completely hyalinized. The proximal tubules were dilated, and their epithelium flattened and atrophic. In places the interstitial tissue was increased, and contained inflammatory cells. Calcium was present either as clumps or as a fine dust in the cells. The clumps were distributed throughout the kidney, but mainly in the cortico-medullary junction; they extended from the tubular cells, and often lay apparently free in interstitial tissue or in the tubular lumen. The fine dust was predominantly in the basement-membrane and the cells of the collecting tubule, and to a lesser

extent in the distal convoluted tubule or in Henle's loops. There was some calcification of the media of a small artery (Dr. M. Hutt).

Discussion

The urine in these two patients with hyperparathyroidism was more dilute than their own plasma, even after dehydration or the administration of pitressin. The excretion of large volumes of hypotonic urine in patients suffering from

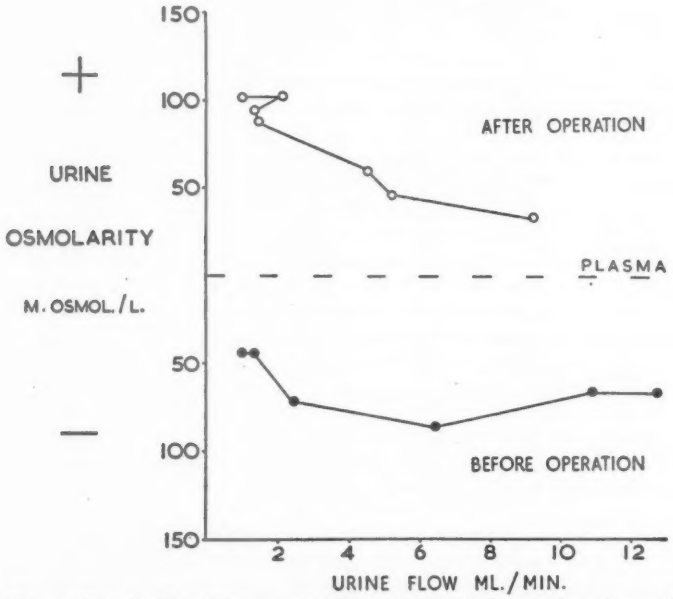

FIG. 2. Case 2. The differences between the osmolarity of the urine and that of the plasma during an infusion of mannitol and pitressin, before and after operation.

hyperparathyroidism has often been described before (Rosenbach and Disqué, 1930; Allan, 1931; Bergstrand, 1931; Elsom, Wood, and Ravdin, 1936; Tibbetts and Aub, 1937; Moulonguet and Lièvre, 1938; Alexander, Pemberton, Kepler, and Broders, 1944; Keating and Cook, 1945; Albright and Reifenstein, 1948; Bruce and Strong, 1955). It has also been reported in other conditions: polyarteritis (Darmady, Griffiths, Mattingly, Spencer, Stranak, and de Wardener, 1955); obstruction of the urinary tract, and myelomatosis (Roussak and Oleesky, 1954); and potassium deficiency (Dustan, Corcoran, and Page, 1956).

In both our patients the ability to form a urine more concentrated than plasma was restored immediately after the parathyroid tumours were removed; at this time the glomerular filtration rate in Case 1 had not changed, and in Case 2 it had risen only to 38 ml. per minute. This suggests that the continuous hypotonicity of the urine before operation was not due to the impaired glomerular filtration rate, but to disturbance of tubular function. This conclusion is supported by the

frequent finding of a normal blood-urea level in such patients (Hellström, 1954); Alexander, Pemberton, Kepler, and Broders (1944) described two patients whose blood-urea was only 18 mg. and 16 mg. per 100 ml. It follows that the hypotonicity of the urine cannot be the result of an osmotic diuresis in the sense referred to by Platt (1952), where a *normal* quantity of solute passing down a reduced number of nephrons probably accounts, in part, for the impairment of concentration in advanced renal failure. Neither is the hypotonicity related to an *increase* in the quantity of solutes being excreted (de Wardener and del Greco, 1955), for the second patient after operation was able to produce a hypertonic urine while excreting solutes at the same rate as before operation (compare the mannitol diureses before and after operation). In the first patient the failure to acidify the urine and the low T_mPAH provide other evidence of failure of tubular function.

The cause of this change in tubular function is not known. The hypotonicity of the urine does not seem to depend simply on the concentration of the serum-calcium, for the blood level of calcium has not always been high in the reported cases. It may be related to the high urinary excretion of calcium, or to a direct effect of the parathyroid hormone. The hormone is known to damage the basement-membrane of the tubule (Baker, Reaven, and Sawyer, 1954). Though this damage may determine where the calcium is deposited, it is clear that this precipitated calcium cannot account for the hypotonicity of the urine. Both our patients recovered from their polyuria very rapidly, and in the second patient the capacity to concentrate the urine had returned to near normal levels at a time when renal biopsy showed widespread deposits of calcium both in and around the tubular cells.

Where in the tubule can a change in function leave the urine consistently hypotonic? There is both direct evidence in rats (Walker, Bott, Oliver, and MacDowell, 1941; Wirz, 1956), and suggestive evidence in man and in dogs (de Wardener and del Greco, 1955; del Greco and de Wardener, 1956), that there is normally a site in the tubule where the fluid is always hypotonic. Fluid obtained from the first part of the distal tubule in the rat kidney is hypotonic whether the urine in the ureter is hypertonic or hypotonic (Walker, Bott, Oliver, and MacDowell, 1941; Wirz, 1956). In the second part of the distal tubule the fluid is hypotonic when the urine is hypotonic, but is isosmotic when the urine is hypertonic (Wirz, 1956). To form hypertonic urine, therefore, tubular fluid must become hypertonic in the collecting tubule. We suggest that the fixed hypotonicity of the urine in hyperparathyroidism represents a failure of the second part of the distal tubules and the collecting tubules to concentrate the hypotonic fluid from the first part of the distal tubules. This implies that the abnormal hypotonicity of the urine could not have existed had not the first part of the distal tubule continued to produce a hypotonic urine in the normal way. The increase in free water obtained with an osmotic diuresis in Case 2 is compatible with this implication. An increase in excretion of free water during an osmotic diuresis also occurs with normal kidneys, either (1) in normal man, if the diuresis is induced at a time when hypotonic urine is being excreted after the

ingestion of alcohol (Kleeman, Rubini, Lamdin, and Epstein, 1955) or (2) in patients suffering from untreated diabetes insipidus (de Wardener and del Greco, 1955). Our patient's kidneys, during an osmotic diuresis, behaved like these normal kidneys in the absence of antidiuretic hormone.

We are indebted to Dr. F. L. Dyson who, having made the diagnosis, referred the first patient to us for study.

Summary

1. Two patients with hyperparathyroidism are described, in whom one of the most prominent symptoms was the excretion of large volumes of urine hypotonic to plasma.

2. Their urine remained hypotonic when they were deprived of fluids, or after the intravenous administration of pitressin, but soon after the removal of their parathyroid adenomata the same procedures made the urine more concentrated than the plasma. At this time, however, the renal blood-flow and glomerular filtration rate of one patient had not changed, and in the other the glomerular filtration rate had only risen from 15 ml. to 38 ml. per minute.

3. In one patient an infusion of hypertonic mannitol and pitressin before operation made the urine more hypotonic, and increased the excretion of free water; with the same procedure after operation the urine remained hypertonic, and there was no increase in excretion of free water.

4. Renal biopsy taken from one patient after operation showed varying changes in the glomeruli, and deposits of calcium particularly in the cells and basement-membrane of the collecting tubules.

5. The evidence suggests that there was a loss of function of the second part of the distal tubule and of the collecting tubules, which diminished the reabsorption of water. This loss of function was independent of the obvious structural damage to the kidney.

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STUDIES IN ACHALASIA OF THE CARDIA[1]

By J. R. TROUNCE, D. C. DEUCHAR, R. KAUNTZE, and G. A. THOMAS

(From Guy's Hospital, London)

With Plate 42

In the first description of the condition which was subsequently to be called achalasia of the cardia, Willis (1679) suggested that it was due to 'an obstruction to the mouth of the stomach either by a tumour or by palsy'. Since then most attention has been directed to the cardia and its cardinal role in the production of the disease. Von Mikulicz (1904) suggested that the condition was due to spasm of the cardiac sphincter, and that the resultant collection of food behind the obstruction was responsible for the hypertrophy and dilatation of the oesophagus, which is characteristic of all but the early stages of the disease. One of the difficulties in accepting spasm as the cause of obstruction was the ease with which tubes could be passed through the cardiac sphincter in such patients, there being apparently no evidence of obstruction. This led Einhorn (1888) to suggest that there was an absence of relaxation of the cardia rather than actual spasm; similar conclusions were reached independently by Rolleston (1896) and Hurst (1913–14). There was no explanation for this failure of relaxation until Rake (1927) reported subacute inflammation, with degeneration of Auerbach's plexus, in post-mortem material from two patients with achalasia of the cardia; these changes were most marked at the cardia, and became less obvious when traced up the oesophagus. In 1929–30 Hurst and Rake expanded their findings, and reported that in 11 cases degenerative lesions in Auerbach's plexus were present. They concluded that the failure of the cardiac sphincter to relax was secondary to this degeneration, which released the cardiac sphincter from the inhibitory effect of the vagus. They coined the term achalasia of the cardia, implying a failure of the cardia to relax. Similar histological findings have been reported by Cameron (1928), Mosher and McGregor (1928), Lendrum (1937), and Gallinaro (1945).

The view advanced by Hurst and Rake, that degeneration of Auerbach's plexus is the primary cause of the condition, has not been universally accepted, and Wooler (1952) believed it to be secondary to the dilatation of the oesophagus. Although mainly the cardia has been studied, abnormalities of the body of the oesophagus have long been recognized: Zenker and von Ziemssen (1878) and Mackenzie (1884) suggested that the condition was due to weakening of the oesophageal muscle. More recently Templeton (1948) in America and Johnstone

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(1950) in this country have described abnormal forms of contraction in the body of the oesophagus, and have shown that in the earlier cases the oesophagus, far from being weak or paralysed, shows considerable activity. As the disease

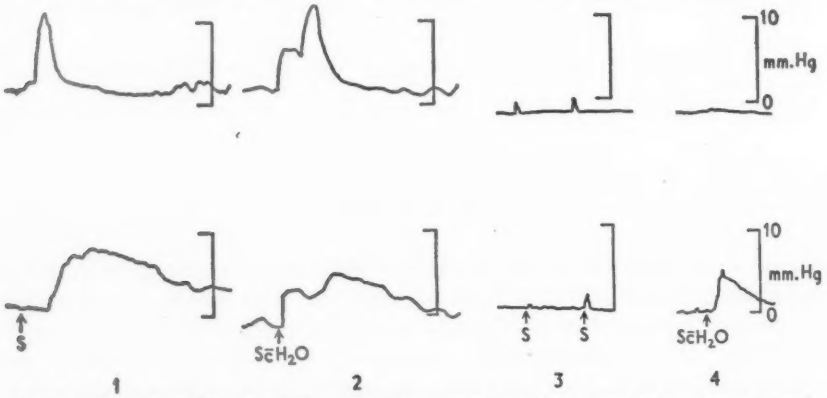

FIG. 1. Intra-oesophageal pressure records. Upper records at four inches, lower records at one inch above the cardia.

1. Normal subject; dry swallow at S. 2. Normal subject; swallow with water at S. 3. Patient with achalasia; dry swallow at S. 4. Patient with achalasia; swallow with water at S. Paper speed 1 mm. per second.

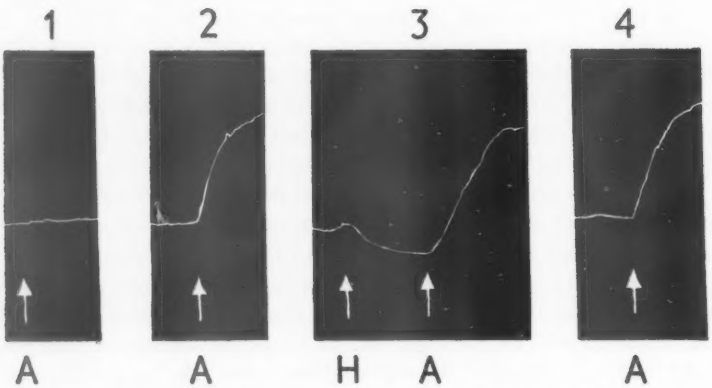

FIG. 2. Patient without achalasia. Longitudinal muscle from the lower end of the oesophagus suspended in 50 ml. bath of tyrode at 37° C.

1. A = acetylcholine 1·0 μg. 2. A = acetylcholine 1·0 μg. after eserine 50 μg. 3. H = adrenaline 50 μg.; A = acetylcholine 1·0 μg.; both after eserine 50 μg. 4. A = acetylcholine 1·0 μg. after eserine 50 μg.

advances this activity tends to become overshadowed by dilatation and tortuosity, but even at this stage powerful contractions of the body of the oesophagus still occur. Butin, Olsen, Moersch, and Code (1953) have studied oesophageal activity. They recorded intra-oesophageal pressure at various levels in subjects with achalasia, and in healthy subjects defined the normal pressure-waves after swallowing. In no case of achalasia did they record a normal complex after deglutition. They concluded that the whole oesophagus is concerned

in the altered mechanism of achalasia. Early in our study of patients with achalasia we also recorded intra-oesophageal pressures, using fine, open-ended, fluid-filled tubes attached to electromanometers. The technique has been described by Dornhorst, Harrison, and Pierce (1954). We were able to confirm the fact that in normal subjects swallowing results in the passage of a peristaltic wave down the oesophagus, but that these waves cannot be recorded in patients with achalasia (Fig. 1).

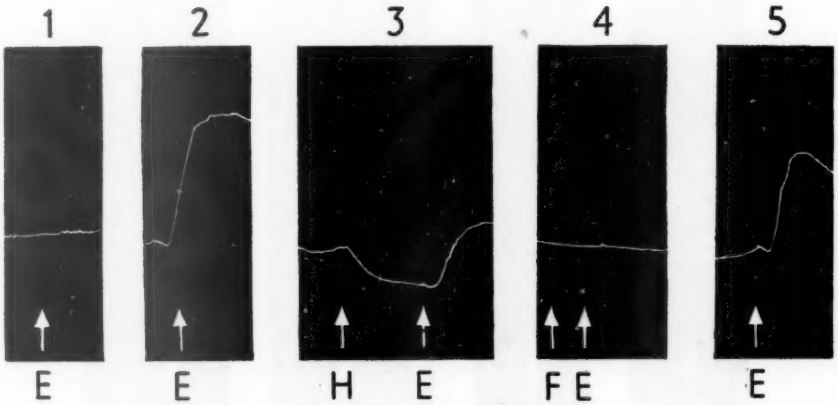

FIG. 3. Subject without achalasia. Longitudinal muscle strips from the lower end of the oesophagus suspended in a 50 ml. bath of tyrode at 37° C.
1. E = nicotine 350 μg. 2. E = nicotine 350 μg. after eserine 50 μg. 3. H = adrenaline 50 μg.; E = nicotine 350 μg.; both after eserine 50 μg. 4. F = hexamethonium 3·0 mg.; E = nicotine 350 μg.; both after eserine 50 μg. 5. E = nicotine 350 μg. after eserine 50 μg.

Barrett (1953) noticed that when a patient with achalasia of the cardia is examined radiologically, it can be seen that below the dilated body the oesophagus narrows down to a point; if a little barium then runs into the stomach, the obstruction will be found in a narrowed segment about 2 to 3 cm. long, and not just at a ring of contraction at the cardia. Oesophageal activity in some of our patients has been recorded by means of cine-radiography (using an electronic intensifying screen) during the swallowing of a thin suspension of barium sulphate. The films so obtained (Plate 42, Fig. 5) show this narrowed segment very clearly. If this region is examined at operation the segment is easily seen, and its muscular walls appear quite normal, in notable contrast with the hypertrophied and dilated oesophagus above. It is clearly at this segment extending upwards from the cardia that obstruction occurs. *Post mortem* this segment is not clearly seen, presumably owing to longitudinal contraction of this portion of the oesophagus. We are here reporting the results of our studies of this narrow segment. Muscle from this area in patients with achalasia, and from the corresponding region in other patients without achalasia, has been examined pharmacologically, biochemically, and histologically, in order to compare its properties in the two groups of subjects, and to confirm or disprove the presence of ganglion-cells in the achalasic segment.

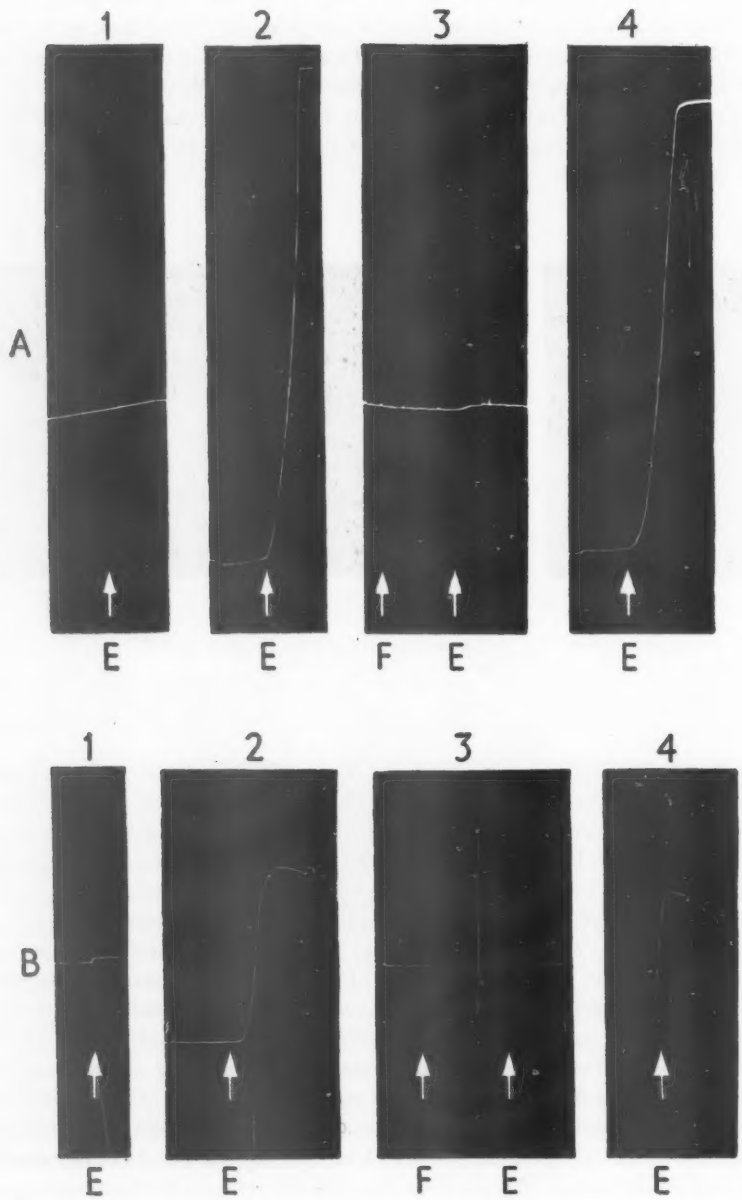

FIG. 4. Longitudinal muscle from the lower end of the oesophagus of (A) a patient with 25 years' history of achalasia, and (B) a patient with four years' history of achalasia.
1. E = nicotine 350 μg. 2. E = nicotine 350 μg. after eserine 50 μg. 3. F = hexamethonium 3·0 mg.; E = nicotine 350 μg.; both after eserine 50 μg. 4. E = nicotine 350 μg. after eserine 50 μg.

Material

During the performance of Heller's operation, longitudinal strips of muscle were removed from the lower end of the oesophagus in seven patients with achalasia of the cardia, and then used in the studies described below. It was not possible to perform all the manœuvres described on every sample of muscle, as sufficient material was not always obtainable. Similar samples were taken

TABLE I

Pharmacological Response of Muscle: Patients without Achalasia

Longitudinal muscle strips from the lower end of the oesophagus were suspended in a 50 ml. bath of tyrode solution

Case number	*Acetylcholine*	*Eserine + acetylcholine*	*Eserine + hexamethonium + acetylcholine*	*Eserine + atropine + acetylcholine*	*Eserine + succinylcholine + acetylcholine*	*Adrenaline*	*Eserine + adrenaline + acetylcholine*
1	+	++	..	..	..	Fall in base line	No block
2	+	++	..	Block	..	Fall in base line	No block
3	+	++	No block	Block	No block	+ (slight)	..
4	0	+	No block	Block	No block	0	..
5	+	++	No block	Block	No block	0	..

Case number	*Nicotine*	*Eserine + nicotine*	*Eserine + hexamethonium + nicotine*	*Eserine + atropine + nicotine*	*Eserine + adrenaline + nicotine*
1	0	+	Block	..	Partial block
2	0	+	Block	..	Partial block
3	0	+	Block	Block	..
4	0	+	Block	Block	..
5	0	0	..	..	..

\+ = Contraction.
0 = No effect.
++ = Increased contraction.
.. = Not done.

Dose of drugs:
Acetylcholine up to 100 μg.
Eserine 50 μg.
Hexamethonium 3·0 mg.
Atropine 50 μg.
Succinylcholine 2·0 mg.
Adrenaline up to 100 μg.
Nicotine 350 μg.

from five patients without achalasia of the cardia, who were having oesophageal resection for other reasons, and these were subjected to the same investigations.

1. *Pharmacological studies. Method.* Oesophageal muscle is very delicate, and rapidly damaged by adverse conditions; great care was therefore exercised in transporting it from the operating theatre to the laboratory. The strips were suspended in oxygenated tyrode solution at 37° C., and contractions were recorded by a lever writing on a revolving smoked drum.

Results. The results in subjects without achalasia are summarized in Table I. It can be seen that the normal muscle contracted with acetylcholine, and that this contraction was increased by eserine (Fig. 2). Nicotine alone gave no contraction, but after the addition of eserine there was a response in four out of five samples, which could be blocked by hexamethonium (Fig. 3). The responses to both acetylcholine and nicotine could be blocked by atropine. The response of the normal muscle to adrenaline was variable. Sometimes there was no response up to a concentration of 1:500,000; on two occasions such a concentration

produced a fall in the base line and a slight decrease in the response to nicotine but not to acetylcholine (Figs. 2 and 3); on another occasion the same concentration yielded a slight elevation of the base line. The findings in subjects with achalasia are summarized in Table II. It can be seen that the muscle strips again responded to acetylcholine, and that the response was increased by eserine and blocked by atropine, but not by succinylcholine. Five out of six samples

TABLE II

Pharmacological Response of Muscle: Patients with Achalasia

Longitudinal muscle strips from the lower end of the oesophagus were suspended in a 50 ml. bath of tyrode solution

Case number	*Acetyl-choline*	*Eserine + acetyl-choline*	*Eserine + hexamethonium + acetylcholine*	*Eserine + atropine + acetylcholine*	*Eserine + succinylcholine + acetylcholine*	*Adrenaline*	*Eserine + adrenaline + acetylcholine*
1	+	++	No block	Block	No block	+ (slight)	..
2	+	++	No block	..	..	..	..
3	+	++	..	..	..	0	No block
4	0	+	..	Block	No block	+ (slight)	..
5	..	+	..	Block	..	0	..
6	+	++	..	Block	..	Fall in base line	..

Case number	*Nicotine*	*Eserine + nicotine*	*Eserine + hexamethonium + nicotine*	*Eserine + atropine + nicotine*	*Eserine + adrenaline + nicotine*
1	0	0	..	..	..
2	0	+	Block	..	..
3	0	+	Block	..	No block
4	0	+	Block	..	..
5	0	+	Block	..	..
6	0	+	Block	Block	..

+ = Contraction.
0 = No effect.
++ = Increased contraction.
.. = Not done.

Dose of drugs: the same as in Table I.

responded to nicotine after eserinization (Fig. 4). The same variety of response to adrenaline was seen as in strips of normal muscle.

These findings suggest that normal muscle from the lower oesophagus behaves like intestinal smooth muscle, responding to acetylcholine, and this response being blocked by atropine. The enhancing effect of eserine argues a mechanism involving cholinesterase. The response to nicotine, blocked by hexamethonium and atropine, suggests the presence of active ganglion-cells, which operate via cholinergic nerve-endings. The failure of one sample to respond to nicotine was probably due to a failure to include ganglion-cells in the muscle strip, or to damage done to the ganglion-cells in removal of the muscle and its transfer to the laboratory. The findings in achalasia of the cardia are substantially the same as those in strips of normal muscle. In the former there is the usual response of unstriped muscle to acetylcholine, which is blocked by atropine, and again there is evidence of cholinesterase activity. Of paramount interest is the response to nicotine after eserine, which occurred in five of the six specimens examined. This response could be blocked by hexamethonium bromide, and indicates the presence of active ganglion-cells within the wall of the oesophagus. The response did not differ from that found in normal muscle.

2. *Biochemical studies.* Kramer and Ingelfinger (1951) have reported increased sensitivity of muscle in the body of the oesophagus to acetyl-β-methylcholine in achalasia, and they regarded this as an example of Cannon's law (Cannon and Rosenblueth, 1936). The explanation, however, might lie in the diminution or absence of cholinesterase in the oesophageal wall. As the increased sensitivity is to acetyl-β-methylcholine, as well as to acetylcholine, it is suggested that the defect might be in the 'true' cholinesterase. It would then be logical to suppose

TABLE III

Cholinesterase Activity in Muscle from the Lower End of the Oesophagus

	μl. CO_2/gm./hr.		
	Acetyl-choline	*Butyryl-choline (pseudo)*	*Acetyl-β-methyl-choline (true)*
Normal	4,495	5,297	410
	3,302	..	558
Achalasia	2,100	3,730	..
	3,262	5,220	..
	..	3,534	..

that a decrease in 'true' cholinesterase was in turn due to degeneration of the peripheral ganglion-cells of the vagus nerve, with subsequent denervation of the oesophagus. If, however, degeneration of ganglion-cells does not occur in the narrowed distal segment of the oesophagus, as is suggested by our observation, then the 'true' cholinesterase content would be normal. It was impossible to study the response of the narrowed segment to cholinergic drugs *in vivo*, owing to difficulties in visualizing this area radiologically, and therefore the cholinesterase-content of muscle from this region, in patients with achalasia and in normal control subjects, was estimated.

Method. The cholinesterase activity was measured manometrically on minced oesophageal muscle by a modification of the method of Ammon (1933–4); the free acid released from the choline ester by the action of cholinesterase liberates CO_2 from the 0·025 M. $NaHCO_3$ medium. Acetylcholine perchlorate, butyrylcholine perchlorate for pseudo-cholinesterase, and acetyl-β-methylcholine for true cholinesterase, were used as substrates. Measurements were made in duplicate, and were corrected for non-enzymatic hydrolysis of the substrate. Activity was expressed in microlitres of CO_2 per gm. per hour.

Results. The results are given in Table III. Although the number of samples is small, it can be seen that there was no obvious difference in the cholinesterase-content of normal and achalasic muscle when butyrylcholine and acetylcholine were used as the substrate. With acetyl-β-methylcholine as substrate the esterase activity was low in normal subjects; in four specimens from patients with achalasia the activity was similar, or slightly higher than in the normal subjects, and in no case was activity absent. The exact readings are not given in the Table, because the amounts of tissue available were so small that results of high accuracy were not possible. None the less, there is good evidence of true

cholinesterase activity in the distal segment of the oesophagus of patients with achalasia. It must be emphasized that these results refer only to the lower end of the oesophagus.

3. *Histology.* The muscle strips were examined histologically in six subjects with achalasia.

TABLE IV

Achalasia: Histological Findings in Muscle from the Lower End of the Oesophagus

Ganglion-cells (A) present in approximately normal numbers; (B) fewer than normal; (C) not seen.

Case number	*Age (years)*	*Length of history*	*Severity of disease*	*Ganglion-cells*	*State of muscle*
2	?	?	Moderate	B	Normal
3	59	26 years	Moderate	B	Normal
4	30	4½ years	Moderate	A	Normal
5	31	4 years	Moderate	B	Normal
6	79	25 years	Advanced	A	Normal
7	54	10 years	Moderate	C	Normal

Method. The material was fixed in formalin and ammonium bromide solution or in absolute alcohol. Multiple sections were cut from each block. Sections were stained with haematoxylin and eosin, and with Giemsa's blood stain in an acid solution, the pH being adjusted to give maximal staining of the chromophilic cytoplasm of the nerve-cells and minimal staining of other tissues.

Results. The quality of the material varied. Most of the muscle had already been immersed in the saline bath for several hours, and a certain amount of change had occurred. The histological examination was largely concerned with the characteristics of the ganglion-cells; it was not possible to give an accurate assessment of the numbers, as the muscle specimens were small, and often only included small areas between the muscle coats where ganglion-cells might be found. Accordingly, they were classified as follows:

A. Ganglion-cells present in approximately normal numbers.

B. Scanty ganglion-cells, usually isolated rather than in groups.

C. No ganglion-cells seen.

The results of histological examination are given in Table IV. It can be seen that in only one specimen were no ganglion-cells seen, and that in two specimens they seemed to be present in normal quantities and with a normal appearance (Plate 42, Fig. 6). In three other specimens they appeared rather scanty, although they were still present in moderate numbers, it being possible to find several cells in a single section. Whether there was a real paucity of cells in these samples, or whether it was due to the inadequate specimen examined, is difficult to judge, although their distribution as single cells rather than as groups suggests that the apparent diminution in numbers was real. There was no apparent correlation between the stage of the disease and the number of cells seen, the most advanced case showing an approximately normal distribution of ganglion-cells. It was difficult to study the morphology of the nerve-cells in

detail, because a certain amount of change had occurred with prolonged immersion in saline. As far as could be seen there was no marked abnormality. The muscle in these specimens appeared normal, but one specimen (Case 6) showed considerable polymorph infiltration, presumably due to oesophagitis.

Discussion

The results of our experiments show that, in patients with moderately severe and advanced achalasia of the cardia, it is still possible to elicit evidence of active ganglion-cells in the narrowed segment at the lower end of the oesophagus in the majority of cases. Such findings are opposed to the view that the failure of the cardia to relax is necessarily due to degeneration of ganglion-cells in that region, with the removal of the inhibitory effect of the vagus. It is usually held that the ganglion-cells in Auerbach's plexus are the peripheral cell-stations of the vagus. If this is so, it is difficult to see how such cells, with presumably cholinergic nerve-endings, could inhibit smooth muscle. Our experiments on the normal oesophageal muscle have shown that stimulation of the ganglion-cells produces a motor and not an inhibitory response. It is therefore doubtful whether degeneration of these cells could lead to a failure of the cardia to relax, unless it is supposed that after denervation the distal segment develops some form of inherent tonic contraction. This might arise from a diminution of cholinesterase at the neuromuscular junctions, resulting in a prolonged and exaggerated response to any acetylcholine which might be produced by remaining nerve-endings or reach this area from other sources. Although our experiments do not completely exclude this possibility, no decrease in activity of true or pseudo-cholinesterase was observed in muscle from the lower segment of the oesophagus.

The role of the sympathetic system at the cardia is not clear. It has been suggested that it might cause contraction of the cardia, and its removal has been advocated as a treatment of achalasia (Knight, 1934). In these experiments we did not obtain any consistent response to adrenergic drugs in either achalasic or non-achalasic subjects; on those occasions when any motor response was obtained it was barely perceptible, whereas relaxation occurred more commonly and was quite marked.

The demonstration of active ganglion-cells in the lower segment of the oesophagus in all but two of the patients with achalasia was surprising, in view of the number of reports of complete or almost complete absence of these cells from this region. It might be suggested that the disease is progressive, and that in time the ganglion-cells would have disappeared in our patients. Such a supposition seems unlikely, for in a patient with advanced achalasia of at least 25 years an approximately normal number of cells was found histologically in a specimen which had previously shown pharmacological activity. It seems probable that ganglion-cell degeneration is confined in certain cases to the dilated portion of the oesophagus above the obstruction, and that previous studies of the histology of this condition have missed this small lower section, which becomes inconspicuous after death.

If changes in the ganglion-cells are not an essential feature of the lower segment of the oesophagus in this disease, it is still necessary to explain why food fails to enter the stomach. It has been assumed that because obstruction occurs at the lower end of the oesophagus, this region must be abnormal, but this assumption may be a *non sequitur*. The factors governing the relaxation of the lower end of the oesophagus are not fully understood, but it is not unreasonable to suppose that, if the function of the main body of the oesophagus were disordered, the lower end might not receive the normal stimulus to relax. There is considerable evidence that the function of the main body of the oesophagus is abnormal in achalasia, and that normal peristaltic waves do not appear. Furthermore, many histological studies have suggested that in this region there is a diminution or absence of ganglion-cells. It is therefore possible that the continued tonus of the lower segment is due to a disturbance in function of the main part of the oesophagus, rather than to any abnormality in the region of the cardia itself. Recent studies by Code, Creamer, Fyke and Olsen, and Kramer and Ingelfinger, which were reported at the International Congress of Gastroenterology, London, 1956, lend support to this hypothesis. Their records suggest that in the normal oesophagus the aspiration of air and of stomach contents into the low-pressure zone of the body of the oesophagus is prevented by 'high-pressure' zones at the top and lower end of the oesophagus respectively. These zones are about 2 to 4 cm. in length, and seem to represent areas of tonic contraction in the oesophageal wall; the lower of these would exactly correspond to the segment we have investigated. During swallowing there is a co-ordinated mechanism which leads to the relaxation of these 'zones' and the passage of a normal peristaltic wave down the body of the oesophagus. In achalasia this mechanism is disturbed, so that there is no peristaltic wave, and relaxation in the lower zone fails to occur. It is easy to see that if the function of the body of the oesophagus were disturbed the whole co-ordinated mechanism might be upset, so that the lower zone, although otherwise normal, would not relax on swallowing.

We wish to thank Dr. J. J. Stevenson and the Dean of the Institute of Urology for the cine-radiography of certain patients, Professor R. H. S. Thompson for the estimations of cholinesterase in muscle, and Mr. G. Blackburn, Mr. R. H. F. Brain, Mr. R. W. Raven, and Mr. N. C. Tanner for the strips of oesophageal muscle.

Summary

1. Longitudinal muscle strips from the lower end of the oesophagus of a group of patients with achalasia of the cardia have been studied, and compared with muscle from a similar region in patients without achalasia.

2. *In vitro* experiments show that strips from both groups of patients behave pharmacologically as smooth muscle, that there is present a mechanism involving cholinesterase, and that in both groups the majority of specimens contain active ganglion-cells.

3. The cholinesterase of muscle samples from both groups showed similar activity.

4. The histological picture was variable, but approximately normal numbers of ganglion-cells were found in two out of six samples from patients with achalasia.

5. The significance of these findings is discussed.

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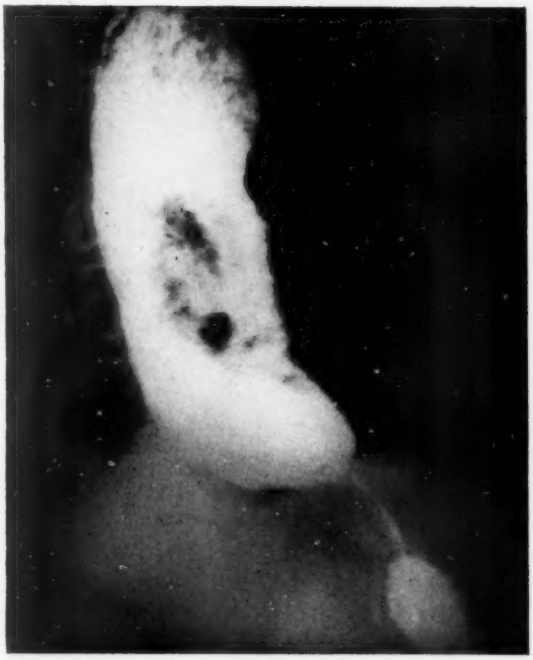

FIG. 5. Radiograph of the lower end of the oesophagus of a patient with achalasia of the cardia, showing the narrowed segment

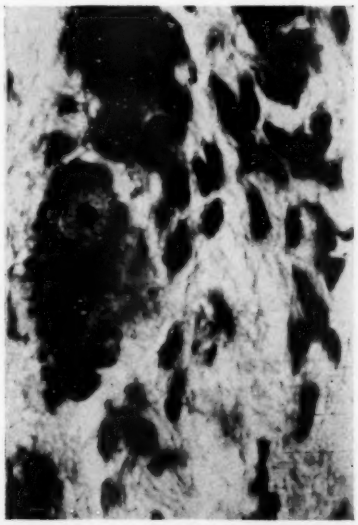

FIG. 6. Details of a ganglion-cell from the oesophagus of a patient with achalasia of the cardia

616.33–007.43

HIATUS HERNIA[1]

A Clinical Study of 200 Cases

By VINCENT EDMUNDS

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With Plates 43 and 44

HERNIATION of all or part of the stomach through the oesophageal hiatus (hiatus hernia), though first described by Morgagni in 1769, has only in recent years become recognized as a fairly common disorder. Even when it is diagnosed, the significance of the finding may be questioned. Radloff and King (1947) were not impressed with the condition as a cause of major symptoms. Of 50 patients they claimed that 68 per cent. had concomitant disease, and attributed symptoms to the hernia in only 30 per cent. Harrington (1948), on the other hand, referred to the condition as 'the masquerader of the abdomen'. He found that in 343 cases an average of three previous diagnoses had been made, and 10 per cent. of the patients had undergone abdominal operations for their symptoms. Many references, even in more recent publications, have made no attempt to discuss the type of hiatus hernia under consideration; this adds to the confusion of the subject and detracts from the value of the observations. Attempts have been made, however, to classify hiatus hernia according to type. The classification of Akerlund (1926) is to be found in many current textbooks. He divided the hernias into: (1) congenital short oesophagus with thoracic stomach; (2) para-oesophageal; and (3) oesophago-gastric. Thoracic surgeons find congenital short oesophagus a rarity (Allison (1951) found one case among 204 patients with hiatus hernia), and at operation in most cases the cardia can be brought down without difficulty to the diaphragmatic level, thus establishing that the shortening was due to muscular contraction. For this and other reasons Allison (1951) proposed that hiatus hernia should be divided into sliding and rolling types. In the former the cardia and a varying amount of the gastric fundus escape into the thorax (Plate 43, Figs. 1, 2). (The name 'sliding' describes the mode of production rather than the habit of the hernias, for while many show clear evidence of reducibility, many others become fixed.) This state of affairs is almost invariably associated with incompetence of the cardia and gastro-oesophageal regurgitation. In the latter type (Plate 44, Fig. 3) a preformed peritoneal sac exists in front of the oesophagus, and into this sac the greater curvature of the stomach herniates by rolling up on itself until, in some cases, only the pyloric antrum protrudes below the diaphragm. Rarely the

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fundus of the stomach remains below the hiatus, the body, antrum, and duodenum herniating into the chest ('upside-down stomach'; Gagliardi, 1952). In rolling hernias the cardiac end of the oesophagus remains anchored in the region of the hiatus. It is not altogether clear whether the hernia is through the hiatus or through an associated defect lying alongside the hiatus (Barrett, 1954–5). The fact that the cardia remains firmly at the hiatus, when such a large portion

TABLE I

Classifications of Hiatus Hernia

Akerlund (1926)	*Allison (1951)*	*Present series*	
Congenital short oesophagus	Nearly all sliding	Sliding	
Para-oesophageal	Rolling	Rolling	
Oesophago-gastric	(1) Para-oesophageal with slide (2) Sliding hernia with para-oesophageal pouch	Combined	

of stomach is in the chest, favours the latter view, and in fact the radiological appearances sometimes suggest the presence of tissue separating the hiatus and the hernia. In Adams and Lobb's (1954) patient a rolling type of hernia was shown at operation to pass through a defect extending from the oesophageal to the aortic hiatus, and they called it an oesophago-aortal hiatus hernia. It is possible that some of the cases of rolling hernia treated conservatively are of this type. In a third group there is radiological evidence of both sliding and rolling hernia (Akerlund's oesophago-gastric type) (Plate 44, Fig. 4). Allison attempted to subdivide such cases still further into those in which a primary 'slide' has been followed by a 'roll', and those in which a rolling hernia has been complicated by an element of 'slide'. The classifications are correlated in Table I. An additional difficulty in forming a clear picture of the disorder is that so many of the reported series have been selected because of their complications or the need for surgical treatment (Allison, 1951; Belsey, 1952*a*; Harrington, 1955).

Object and Scope of the Present Investigation

The present clinical study of hiatus hernia was undertaken in an attempt to clarify the picture in a series of cases unselected by surgical or other bias, to relate this picture to the anatomical lesion present, to establish the relative importance of the condition as a source of symptoms, to review some of the complications, and finally to discuss the best methods of treatment. The nomenclature used is that suggested by Allison (1951), with the exception that his third group has not been subdivided (this seemed impossible in most cases as

well as artificial), but presented as 'combined' hernias. The cases comprise a consecutive series of 204 patients found to have hiatus herniation on routine radiography for dyspepsia or bleeding. The series was collected between January 1951 and March 1955, and with few exceptions includes all the cases diagnosed in the Central Middlesex Hospital over that period.

Incidence

Radiological. Reference to the radiological incidence in this hospital is informative (Table II), and shows that between 1947 and 1951 the condition was

TABLE II

Radiological Incidence of Hiatus Hernia compared with Ulcer and Gall-bladder Disease

	1947	*1948*	*1949*	*1950*	*1951*	*1952*	*1953*	*1954*
Hiatus hernia	5	10	14	38	61	56	54	53
Gastric ulcer	158	184	153	134	173	131	170	145
Duodenal ulcer	301	295	416	521	672	520	494	494
Gall-stones or loss of gall-bladder function	..	..	..	..	..	143	169	221
Total new barium meals	1,120	1,142	1,472	1,787	1,759	..	..	..
Total cholecystograms	..	..	..	..	..	690	780	1,076

being diagnosed with increasing frequency, although the number of examinations performed for upper abdominal dyspepsia remained fairly constant. Since 1951 the figures for hiatus hernia have changed little, indicating that a standardized technique is probably revealing the majority of such abnormalities.

Type and sex. Table III shows the relative incidence of the three types of hernia in the present series, and their sex distribution. The series contains four cases in which insufficient radiological data were obtained for accurate classification. Of the remaining 200 it is seen that 145 (72·5 per cent.) were of the sliding type, and that 107 of these occurred in women. This finding is in keeping with the experience of other authors, that the sliding hiatus hernia in women is the commonest form of this lesion. Tables III and IV show that in the present series hiatus hernia was four times as common in women as in men. It is also apparent that, in contrast to the sliding hernia in women, which is the commonest variety met with, the rolling hernia in men is a rarity, the ratio between these two extremes being 35 to one.

Age. (1) *Sliding hernia.* Of the women, the youngest seen was 21 and the oldest 81 years old, though 85 per cent. were between the ages of 46 and 75. A smaller group of women, mainly pregnant, were between 21 and 40 years of age when seen. Over 50 per cent. of the women first experienced symptoms at or after the menopause (46 to 65 years). Forty-five per cent. gave a longer history, going back to pregnancy or late childhood. The men presented a similar range of age. (2) *Rolling hernia.* There were insufficient men to warrant analysis, but 90 per cent. of the women seen were between the ages of 46 and 75 years. The youngest experienced initial symptoms at the age of 21. (3) *Combined hernia.* Of the women, the youngest first experienced symptoms during pregnancy at

22 years of age. The oldest was first troubled at the age of 73. Over 50 per cent. were at least 50 years old when their dyspepsia began.

The length of history showed considerable variation in all groups. In the 'sliding' (S) group one of the women had experienced symptoms for 39 years, and another for 50, and one man gave a 40 years' history. Nevertheless patients with the sliding lesion tended to give a fairly short history, owing, doubtless, to

TABLE III

Sex Incidence of Various Types of Hiatus Hernia

Type		Number of patients		Female:male ratio
		Female	Male	
Sliding	145	107	38	2·8:1
Rolling	35	32	3	10:1
Combined	20	19	1	19:1
Unclassified	4	3	1	..
Total	204	161	43	3·7:1

the more acute nature of their dyspepsia. Over 30 per cent. of the women in this group gave only a year's history (and two-thirds of these less than a year); such a short history was given by only 10 per cent. of the women in the 'rolling' (R) group. Furthermore, while 50 per cent. of the women in the S group had only

TABLE IV

Ratio of Sliding to Rolling Hernias in Women and Men

Both sexes	3·4:1
Women	3·3:1
Men	13:1

a two-year history, a similar percentage in the R group had experienced their symptoms for four or more years. In the 'combined' (C) group the length of history varied from a few months to 32 years.

Symptomatology

The main complaints were of epigastric pain, heartburn, regurgitation of food or acid, or both, vomiting, flatulence, dysphagia, haematemesis, and symptoms referable to anaemia. Their relative incidence in the main groups is shown in Table V.

1. *Epigastric pain.* Abdominal symptoms, usually centred in the epigastrium and one or other hypochondrium, were not infrequent, arising in 49 per cent. of the rolling hernias, 31 per cent. of the sliding, and 25 per cent. of the combined. Occurring after food, also sometimes at night, with an ulcer-like regularity, they often misled clinicians in the earlier stages of investigation. Further questioning would reveal, however, that the epigastric pain was in most instances associated with a retrosternal distress, likewise related to the taking of food. This deep-seated retrosternal discomfort was recognized by most patients as heartburn, though a few considered that there were differences.

2. *Heartburn.* While it was sometimes difficult to be certain that patients

were referring to heartburn, this symptom usually appeared to consist of a burning discomfort, central in the chest, either stationary, or spreading upwards to the throat and often to the jaws and ears, through to the back between the scapulae, and occasionally down one or other arm. These were the extremes of distribution, and all grades of severity and spread were met. Nearly 90 per cent. of the women and over 60 per cent. of the men (an overall average of 78 per cent.) in the S group were troubled by heartburn. The overall figures in the

TABLE V

Showing the Principal Presenting Symptoms and their Relative Frequency

Symptom	Type of hernia: Sliding *	Sliding %	Rolling *	Rolling %	Combined *	Combined %
Regurgitation	1	81	5	48	2	80
Heartburn	2	78	2	60	2	80
Flatulence	3	72	1	69	1	94
Vomiting	4	48	2	60	4	47
Dysphagia	5	41	8	16	5	40
Epigastric pain	6	31	4	49	7	25
Haematemesis or melaena	7	15	6	17	6	35
Anaemia	8	0	7	17	8	0

* Order of frequency in type.

R and C groups were 60 per cent. and 80 per cent. respectively. Together with epigastric pain, heartburn was related to the taking of food, occurring usually 15 to 30 minutes after the meal, though not infrequently delayed for one or two hours. The size of the meal would often determine the onset of symptoms, small meals being taken with impunity, but larger ones causing inevitable dyspepsia. In some patients, however, the nature of the food rather than the size of the meal was the decisive factor. Almost all foods were incriminated, though in the main roasts, fried foods, pastries, and sweets seemed most liable to cause upset. Movements, particularly after a meal, would often produce heartburn, as would sitting in an easy chair. Bending and stooping were a source of trouble to nearly 80 per cent. of the women and 50 per cent. of the men in the S group. 'It is murder putting my shoes on, doctor' was a typical comment. Many women with a sliding hernia found that they could no longer perform simple household or gardening duties which entailed stooping, though in a kneeling posture they could often continue in reasonable comfort. Heartburn was particularly troublesome at night in 78 per cent. of the cases of sliding hernia, 34 per cent. of cases of rolling hernia, and 65 per cent. of those of the combined lesion. For some patients heartburn at night was the only symptom, and for many it was the most distressing feature. Severe pain would occur either soon after retiring, especially when a meal had been consumed shortly before, or else the sufferer would awake in the small hours with severe pain. Relief might be gained by drinking water, or by taking an alkaline powder, usually sodium bicarbonate, though getting up and walking round the room was often the only way to ease the discomfort. Heartburn seemed to arise slightly more frequently when the

patient lay on the right side, though a few patients found lying on the left side more liable to provoke it, while for some it was impossible to lie on either side in comfort.

3. *Regurgitation* was met with in all groups, being the commonest symptom in sliding hiatus hernia (in 81 per cent.: 90 per cent. of women and 50 per cent. of men). Confusion often arose in the patient's mind between reflux and vomiting, the latter complaint being found on closer questioning to be an effortless reflux. Regurgitation was found to follow closely the pattern of heartburn in its relationship to meals and posture; occasionally, however, the symptoms of free regurgitation were met in the absence of heartburn. The patient would notice mouthfuls of partially digested or undigested food, usually with an acid flavour, especially when moving about after a meal. Acid regurgitation, occurring in a similar manner, usually to the accompaniment of heartburn, was especially noticed at night, when the sufferer might awake coughing to find the throat, and occasionally the nose, full of 'scalding' fluid. Such free reflux was not met in association with a rolling hiatus hernia.

4. *Vomiting.* The figures recorded for vomiting are not necessarily wholly reliable (S, 48 per cent.; R, 60 per cent.; C, 47 per cent.), because of confusion with regurgitation in the patients' minds. An attempt was made to exclude all 'vomiting' which had not been preceded by nausea. Some patients would make themselves vomit by pharyngeal stimulation in order to relieve their retrosternal discomfort or dysphagia. Several patients complained that they had always tended to vomit easily, ever since childhood. Biliousness in youth was also a feature, and travel sickness not uncommon.

5. *Dysphagia.* Some grade of dysphagia was met in all groups (S, 41 per cent.; R, 16 per cent.; C, 40 per cent.).

(1) Many patients noticed that at the beginning of a meal the first mouthful would stick in the lower sternal region. They would have to abandon their meal until the bolus had passed or had been ejected by self-induced vomiting. This disability was usually found in association with a hernia of appreciable size, that is, rolling or combined. Its causation is obscure, but possibly it was due to the relationship between the hernia and the lower end of the oesophagus, gaseous distension of the former temporarily obstructing the latter; thus some patients found relief in belching.

(2) Many complained that after a meal the feeling of 'a lump as though I have swallowed a sweet' persisted in the centre of the chest.

(3) In yet a third group a retrosternal soreness was experienced when all but the blandest of foods were swallowed, 'as though something were scratching inside'. This symptom was only once met with in a case of rolling hiatus hernia, but was the commonest type of swallowing difficulty in sliding hernias.

(4) A few patients experienced occasional difficulty in swallowing if they took their food too rapidly. This symptom was an early stage of (5).

(5) True obstructive dysphagia was met in seven patients, who showed the presence of some degree of oesophageal narrowing. It was never found in cases of rolling hernia. Where narrowing was considerable only fluids and semi-solid

foods could be taken. In one patient an episode of absolute oesophageal obstruction resulted after attempting to eat an orange. The obstruction was successfully relieved eventually by oesophageal lavage, a bolus of orange pith being regurgitated. In some of these cases symptoms were indistinguishable from oesophageal carcinoma.

6. *Flatulence* is a vague symptom which occurs in a diversity of medical complaints, not all gastrointestinal. While the principal symptom in the rolling (69 per cent.) and combined hernias (94 per cent.), it was also very common with the sliding lesion (72 per cent.). It was usually accompanied by abdominal

TABLE VI

Incidence of Haematemesis or Melaena in Various Types of Hiatus Hernia

Type of hernia	*Sex*	*Haematemesis*	*Melaena*	%
Sliding	F	12	1	15
	M	8	0	
Rolling	M and F	4	2	17
Combined . . .	F	6	1	35

distension, and both were often eased by belching. Not infrequently, however, an attempt at belching would produce heartburn. The severest forms of flatulence were met with in rolling hernias, in which the discomfort might be felt not only in the epigastrium and left hypochondrium, but also in the left chest. This form of flatulence would sometimes arise at the commencement of a meal, and all attempts at eating would have to be abandoned until the wind had dispersed.

7. *Haematemesis and melaena.* Episodes of bleeding were not uncommon, and Table VI shows their incidence. It will be noticed that more than a third of the patients with the combined lesion gave a history of gastrointestinal haemorrhage (usually haematemesis) at some time. In recording these facts it is not claimed that the hernia was necessarily the underlying cause of the bleeding. Seventeen patients were first seen because of an episode of bleeding, a hernia being demonstrated for the first time during the subsequent investigations. In 10 of these 17 the absence of other lesions such as duodenal ulcer, the nature of the symptoms, or the radiological evidence, tended to incriminate the hernia as the source of the bleeding. It was noted that four of these patients had a large gastric pouch in the hernia. This is in keeping with the experience recorded below, that anaemia also is commonest when there is an appreciable gastric herniation (that is in the R or C groups), and not to be expected with the sliding lesion. It is concluded that bleeding of any consequence usually occurs with large hernias. Other causes should be excluded when a large haemorrhage occurs with a small or dubious and otherwise symptomless hernia. Bleeding when met with in association with sliding hernia was mild, consisting in the regurgitation or vomiting of mouthfuls of pinkish, blood-stained froth, acid, or food. Bleeding may arise in such cases as a result of ulceration in the gastric hernia, but it is more usually the result of oesophagitis, and the symptoms are correspondingly oesophageal in character.

8. *Anaemia.* Lethargy, shortness of breath, and palpitations were the presenting symptoms in 17 per cent. of the cases of rolling hernia. These symptoms

were never mentioned in either of the other groups. Haemoglobin estimations were performed in all cases in which anaemia was suspected on clinical grounds. An arbitrary level of 80 per cent. (12 gm. per 100 ml.) of haemoglobin was selected, and all lower readings were recorded as showing some grade of anaemia. On this basis very little anaemia was discovered in the S group. The percentages among women in the other groups were: R, 55 per cent.; C, 28 per cent. The anaemia was invariably of the hypochromic iron-deficiency variety, and responded to oral iron. The grade of anaemia in the R group was often severe, haemoglobin being in seven cases 50 per cent. or less and in three 40 per cent. or less. Tests for occult blood in the stools, in six patients with rolling hernias who showed moderate to severe grades of anaemia, gave a positive result in five.

9. *Miscellaneous.* A method of presentation which should be mentioned was the accidental discovery in two cases of a large rolling hiatus hernia on routine X-ray of the chest. A cystic shadow was demonstrated behind and to the right of the heart. Such a chance discovery serves to emphasize the comparative, and sometimes complete, absence of symptoms with this type of hernia. Cough is another uncommon symptom associated with hiatus hernia. In one case, not in the series, a dry, irritating cough was present, especially at meal times, and it was suspected that distension of the sac in some way caused a reflex cough. In one other patient, however, who had a combined hiatus hernia, the cough was quite obviously related to change in posture. On X-ray screening it was noted that bouts of coughing coincided with episodes of free gastro-oesophageal regurgitation of barium to the upper end of the oesophagus.

Physical Findings

The principal signs looked for in these patients were the presence or absence of obesity, abdominal tumour, spinal deformity in the shape of kyphoscoliosis, anaemia, or associated inguinal hernia. Borborygmi heard in the chest were noted. The results in the various types of hernia are shown in percentages in Table VII.

(1) *Obesity.* Overweight and the extremes of obesity were most frequently found with the sliding and combined lesions. (2) *Abdominal tumours.* In 11 patients symptoms arose suddenly during pregnancy. One had a combined hiatus hernia; the remaining 10 had sliding hernias (9 per cent. of the S group). Two other patients were discovered in the gynaecological department. They had large ovarian cysts and sliding hiatus hernias (Plate 43, Fig. 2). (3) *Kyphoscoliosis.* Noticeable spinal deformity occurred with considerable frequency in the R (60 per cent.) and C (40 per cent.) groups (Plate 44, Fig. 4). In one patient the condition was due to old tuberculous caries of the dorsal spine, while in another 'curvature' had been present since birth. (4) *Anaemia* has already been discussed under symptomatology. (5) *Associated hernias.* In women it was found that inguinal hernia was associated with a rolling more frequently than with a sliding hernia, in spite of the preponderance of the latter lesion. (6) *Borborygmi.* Bowel sounds were heard anteriorly or posteriorly over the centre of the chest

in 50 per cent. of the female R group, 7 per cent. of the female C group, and 8 per cent. and 11 per cent. of the male and female S groups respectively. Occasionally the act of swallowing was required to initiate a cadence of borborygmi.

Associated Diseases

In 24 cases (12 per cent. of the series) the following associated disorders came to light: carcinoma of the oesophagus, two cases; carcinoma of the stomach, two cases; carcinoma of the bronchus, one case; gastric ulcer, three cases; duodenal ulcer, 11 cases; gall-stones, four cases; diverticulosis coli, one case,

TABLE VII

Physical Findings

Type of hernia	*Number of patients*	*Sex*	*Obesity*	*Abdominal mass*		*Kypho-scoliosis*	*Anaemia*	*Other hernias*	*Borbo-rygmi*
				Preg-nancy	*Ovarian cyst*				
Sliding	107	F	66%	9%	2% (2 cases)	20%	3%	6%	11%
	38	M	50%	..	..	20%	8%	50%	8%
Rolling	32	F	36%	0	0	60%	55%	16%	50%
	..	M	..	..	..	..	..	..	..
Combined	19	F	85%	1 case	0	40%	28%	12%	7%
	..	M	..	..	..	..	..	..	..

producing recurrent severe melaena. In only six of these patients (3 per cent. of the series) was the coexistent disease clearly responsible for the symptoms; in 97 per cent. of the patients the hiatus hernia could explain some or all of the dyspeptic symptoms present. Among these 97 per cent., however, in four patients the appearance of symptoms was clearly related to a more serious underlying condition such as gastric carcinoma or an ovarian cyst, although the symptoms themselves were hernial in type and origin. The 11 cases of duodenal ulceration showed the normal sex distribution, there being five cases among 158 women and six among 42 men, giving a normal male:female ratio for duodenal ulcer of 4·5:1. In view of a possible relationship between sliding hiatus hernia and gall-bladder disease, the cases were reviewed from this standpoint, and in a small series routine cholecystograms were performed. Twenty-three investigations revealed 21 normal gall-bladders, one with good function but a stone, and one with poor concentration. In addition gall-stones were demonstrated in three other patients during the course of their barium-meal examinations. Seven further patients gave a history of cholecystectomy. Of these seven, three were definitely helped by the operation. The remaining four continued to experience identical symptoms, although in two cases the operation had been carried out 25 and 15 years previously. Their complaint appeared to be reflux oesophagitis.

Precipitating Factors

Patients themselves related the onset of their symptoms to a variety of causes, such as rapid gain of weight over a short period, pregnancy, rest in bed, a tight belt, or moving heavy furniture. The types of hernia found in these cases are shown in Table VIII. In all of these factors an increase in intra-abdominal

pressure is involved, and the resulting hernia was either sliding or combined, but not rolling. A possible relationship between a history of childbirth and herniation was sought, and the relevant figures are shown in Table IX. It will be seen that they are comparable in the three groups. There was a high incidence of multiparity in the combined group, but the numbers were not sufficient to be significant.

TABLE VIII

Possible Precipitating Factors in Hiatus Herniation

Hernia related by patient to:	*Number of cases*	*Type of hernia*		
		Sliding	*Rolling*	*Combined*
Gain of weight	8	8	0	0
Pregnancy	5	4	0	1
Ovarian cyst	2	2	0	0
Prolonged rest with fractured femur	1	0	0	1
Wearing tight belt	1	1	0	0
Moving furniture	1	1	0	0
Add: patients seen first in pregnancy	10	9	0	1
Total	28	25	0	3

Special Investigations

Reference has already been made to haemoglobin estimations, and to examination for occult blood in the stools of a few selected patients. Fractional test meals were also carried out in selected cases. No further reference will be made to these investigations. Comment must be made, however, on radiological techniques. In the process of assigning the cases to their correct anatomical category, many patients were radiologically examined in a special screening session with the author. The particular points looked for included: (1) The presence or absence of any supradiaphragmatic pouch of stomach in the upright position. (2) The apparent location of the cardia, whether at the apex of the gastric pouch, below it but above the hiatus, or at the hiatus itself. (3) The presence of gastro-oesophageal regurgitation. With the sliding hernia this was best demonstrated with the patient standing in the lateral position and bending well forward, if necessary, with the knees bent in order to increase intra-abdominal pressure. Many patients referred for examination with suggestive symptoms but negative X-rays were found, when screened in this position, to have an obvious hernia with free hiatal incompetence. It was found important to fill the stomach with barium for this manœuvre to succeed. Occasionally a deep breath or the act of swallowing, in the head-down position, would produce a knuckle of stomach above the diaphragm and permit the regurgitation of barium into the oesophagus. A negative X-ray result for sliding hernia was of little significance if only the prone or Trendelenburg positions had been used. It is felt that, where symptoms are suggestive, the forward bending position should always be employed. In examining patients for reflux from a rolling hernia, however, this posture had little value, since the cardia and oesophagus were then uppermost. For these hernias the prone position, in which the cardia lies posteriorly, was employed, and was of value if any reflux at all was present.

Table X shows the frequency with which gastro-oesophageal regurgitation was demonstrated in the various types of hernia. Barium-swallow examination proved an unreliable means of investigating cases of painful dysphagia due to oesophagitis, quite severe grades escaping detection. Bread soaked in barium and then swallowed was sometimes of value in these cases, by provoking painful spasm at the site of the oesophageal lesion. It was noticed that patients could indicate with extraordinary accuracy the location of this spasm.

TABLE IX

Hiatus Herniation and History of Childbirth

Births	*Type of hernia*		
	Sliding	*Rolling*	*Combined*
None	18%	18%	0
One	28%	36%	25%
Two or more	54%	46%	75%
Three or more	27%	29%	50%
Six or more	*9%	7%	12%

* Two patients each had 10 children.

TABLE X

Type of hernia	*Radiological reflux*
Sliding	93%
Rolling	42%
Combined	85%

Complications

Of the possible complications arising as a result of hiatus herniation, the present series included haematemesis and melaena, anaemia, and oesophageal stricture. There were no cases of perforation or strangulation. Reference has already been made to the cases of bleeding and anaemia. Radiological examination revealed 13 patients (6·5 per cent.) with narrowing of the lower oesophagus. All these cases occurred in the sliding hernia group, of which they constitute 9 per cent. The narrowing was due to spasm, simple stricture, or carcinoma.

1. *Spasm.* Localized oesophageal spasm, proximal to the cardia, when present, was associated with painful or obstructive dysphagia. The condition could be accentuated by administering bread soaked in barium. There were four cases, three in women and one in a man, and the condition improved as the symptoms were controlled. No patient developed organic stenosis.

2. *Simple stricture* was seen in seven patients (four women and three men), making together 5 per cent. of the S group (8 per cent. of the men and 4 per cent. of the women). Two of the three men had duodenal ulcers in addition to the hernia. All these patients were first seen complaining of dysphagia of three to 24 months' duration. Close questioning failed in most cases to reveal any long history of heartburn, regurgitation, or vomiting. In several patients, indeed, the onset was with an acute attack of retrosternal pain and dysphagia, and in one case with haematemesis; the cause was presumably acute peptic oesophagitis, making the starting point of the stricture. In two patients, however, the

history was of progressive dysphagia with loss of weight, and only the radiological appearances and negative biopsy excluded an oesophageal carcinoma. There was a notable absence of obesity in this group. The sliding hiatus hernia in all these cases showed on X-ray as a very small sac above the diaphragm. Regurgitation was demonstrated in three of the seven cases, the stricture presumably forming a false cardia in the remaining cases and hindering free reflux. Heartburn and regurgitation, however, occurred in two women whose strictures were dilated.

3. *Oesophageal carcinoma.* Two cases were met with in the present series (1 per cent. of the whole series and 1·3 per cent. of the S group), both associated with a sliding hiatus hernia. One was a man whose history was mainly that of progressive dysphagia with (in addition, on questioning) heartburn and regurgitation. X-rays showed a small hiatus hernia and a somewhat dilated oesophagus, with a smooth stricture involving its lower two inches. The other, a woman with a sliding hiatus hernia and reflux oesophagitis, failed to respond to medical measures. Surgical repair of the hernia was advised, and barium-swallow examination preparatory to operation revealed an oesophageal neoplasm. In a third case, not included in the series, a smooth oesophageal stricture associated with a sliding hernia was shown at operation to be malignant. These cases are recorded because of the impossibility of distinguishing the condition from benign stricture purely on clinical or radiological grounds. All cases of oesophageal stricture, arising in the absence of known trauma or corrosive action, must be submitted to oesophagoscopy and biopsy. Even then it may not always be possible to make a firm diagnosis.

Treatment

1. *Medical*

The management of the cases was in the first instance on medical lines.

(1) *Sliding hernia. Weight reduction.* Where obvious obesity was a feature (66 per cent. of the female patients) a strict reducing diet was advised. Patients in whom the onset of symptoms had coincided with a period of rapid gain in weight lost their symptoms completely, and it then became impossible to demonstrate their hernia and regurgitation radiologically. Some seemed to have a critical weight level below which their symptoms disappeared quite suddenly. These hernias were obviously truly sliding and reducible. *Meals.* Most patients found small meals more easily digested and less liable to give rise to heartburn or regurgitation. There were exceptional patients who could eat a large meal with impunity, and yet have severe heartburn after a cup of tea. Apart from patients receiving a reducing diet, no foodstuffs were prohibited unless they were known to cause discomfort to the subject concerned. In cases where oesophageal symptoms were troublesome, however, a special bland diet was prescribed. The timing of the last meal at night was very important, and could make the difference between a sleepless night and complete freedom from distress. Large meals, taken less than four hours before retiring, were discouraged. *Posture.* The importance of maintaining an upright posture, particularly after

meals, is self-evident. Many women found that, while stooping would bring on their symptoms, kneeling would not. The use of long-handled household and garden equipment was encouraged. Patients experiencing nocturnal discomfort (most of those in the S group) were advised to sleep with the head and shoulders well raised. Extra pillows were usually unsatisfactory, and resulted only in an uncomfortable night or a stiff neck in the morning. Raising the head of the bed nine inches was far more satisfactory. Wooden blocks, bricks, old books or directories, or a chair, were used with advantage in all such cases, and in most gave complete relief. *Antacid.* Aluminium hydroxide, either in emulsion or in tablet form, was found to be most valuable in easing the discomfort of heartburn. Patients were advised to take a dose whenever necessary, and also half an ounce of the emulsion immediately before retiring.

(2) *Rolling hernia.* In contrast to the S group, these patients often required no treatment. It is surprising to meet a patient with well over half of the stomach in the chest, but no symptoms. Symptoms were rarely so severe as in the S group but, when present and related to posture, were dealt with on the lines outlined above. Flatulence, not infrequently associated with an ache in the left chest, was best relieved by small doses of sodium bicarbonate. Iron-deficiency anaemia was the condition most frequently demanding treatment (55 per cent.), and invariably responded to oral iron. In view of the recurrent nature of the anaemia it was deemed advisable to prescribe a small daily dose of iron, such as ferrous sulphate gr. 3, to these patients, to be taken indefinitely, and on such a régime the anaemia showed no tendency to recur.

(3) *Combined hernia.* The patients with a combined hernia in the main manifested symptoms characteristic of a sliding hernia, and were dealt with on the same lines. Those with anaemia received iron.

(4) *Pregnancy.* The cases which occurred in pregnancy require separate comment. They were treated along similar lines. Complete relief was not to be expected until after delivery, but in most cases improvement was achieved with small meals, the use of posture, and antacid. A few patients required admission to hospital because of persistent vomiting or heartburn during the last four to six weeks of pregnancy. The effect of delivery on the dyspepsia was most noticeable (Plate 43, Fig. 1*b*). Eleven patients with hiatus hernia were first seen in pregnancy. Of eight regarding whom post-partum details are available, five lost all symptoms, two were considerably improved, and one was no better. A hernia was still demonstrable in only one of the five 'cured', in one of the two improved, and in the one who was no better.

2. *Surgical*

The indications for surgery were taken to be failure of medical means adequately to control symptoms, or the presence of some complication. In the present series 33 patients (16·5 per cent.) have so far come to surgery; 23 of these (five men and 18 women) had sliding hernias, eight women had rolling, and two women combined hernias. In 23 patients transthoracic repair of the hernia was performed; in one, who had a duodenal ulcer, a partial gastrectomy was also

carried out. Five of these patients (21 per cent.) had a recurrence of reflux oesophageal symptoms after six months of freedom. All these five had shown some gain of weight (in one patient more than one and a half stone) as a result of their absent dyspepsia and improved appetite. Barium-meal examination, however, showed a recurrence of the hernia in only three patients, and in two of these the hernia was known to be still present on X-ray examination immediately after operation (an empyema had complicated the thoracotomy in one case). In a sixth patient symptoms, especially vomiting, persisted in spite of repair, and further X-ray studies showed linitis plastica. In a seventh case repair of a sliding hernia for recurrent haematemesis and melaena has been followed by further bleeding, in spite of successful reduction.

In four patients, three of whom had duodenal ulcers in addition to a sliding hernia, partial gastrectomy proved a satisfactory treatment. One patient, with a rolling hernia and symptoms resembling achalasia of the cardia (dysphagia, retrosternal heaviness, and occasional vomiting), gained complete relief after a left phrenic crush. In three patients, in whom oesophageal stenosis had developed, resection of the stricture, fundus, and upper two-thirds of the gastric lesser curvature was performed, followed by end-to-end anastomosis between the oesophagus and reconstructed stomach. The results have so far been successful. As an alternative to resection for stricture, the lesser procedure of dilatation has been tried. After preliminary oesophagoscopy and biopsy, when the stricture was benign, an attempt was made to dilate it gently with gum-elastic bougies. In one patient one such dilatation was sufficient. In another case (and in two others not in the series) the patient herself, after 18 months, still dilates the stricture up to size 22 or 24 every few days, using gum-elastic bougies softened in warm water. All patients so treated have noticed some temporary increase or return of their heartburn, for which they take aluminium hydroxide and adopt the usual medical régime for sliding hiatus hernia, but all have experienced great improvement in swallowing.

Discussion

Incidence. The true incidence of this fairly common condition may never be known, because its presenting features are so varied, symptoms often mild, atypical, or absent, and radiological findings often inconsistent. Mobley and Christensen (1956) computed the annual incidence to be between 0·5 and 0·8 per 1,000, with a prevalence of five per 1,000. Cernock (1953), among 200 patients over the age of 50 and having no gastrointestinal symptoms, found three (1·5 per cent.) with hiatus hernias. In infants Carré, Astley, and Smellie (1952) found the incidence of the condition to be one-fifth of that of pyloric stenosis. It is easier to assess its radiological prevalence, though even here there is difference of opinion. Branwood (1948) recorded 15 cases (5 per cent.) in 300 patients attending hospital with gastrointestinal symptoms. Bockus (1943) quoted and condemned the vigorous radiological methods used by Schatzki (1932), who claimed that hernias could be found in 70 per cent. of patients over the age of 60.

Hodson (1954) stated that with appropriate technique gastro-oesophageal regurgitation and sliding hiatus hernia could be demonstrated in about 5 per cent. of barium meals. Nevertheless, many radiologists are aware of great difficulty in consistently demonstrating even known hernias with established symptoms. Many cases in the present series were shown only after repeated and painstaking examinations had given negative results. Johnstone (1954) suggested that

TABLE XI

Classification of Hiatus Hernia

Allison (1951)			*Present series*	
Para-oesophageal	21		Rolling	35
Para-oesophageal with slide	7	13	Combined	20
Sliding hernia with para-oesophageal pouch	6			
Sliding hernia	170		Sliding	145
Congenital short oesophagus	1			
Indeterminate	1		Insufficient data	4
In 204 patients, a total of 206 hernias*			Total	204

* Recurrence of hernia and second operation in two cases.

fatigue might be a factor, and that possibly such investigation should be conducted in the evening. In our experience one hiatus hernia was demonstrated in every 30 barium meals (3·3 per cent.), as compared with one in 10 for gastric and one in 2·6 for duodenal ulcers. The reported sex incidence varies, but most observers agree on the female preponderance. Stensrud (1954) reported 42 cases, 30 in female and 12 in male patients. Many of the larger series, with a surgical bias, give a distorted picture of the sex ratio, and this difficulty is also encountered in attempts to establish the incidence of the various types of hernia. The present series is compared with that of Allison (1951) in Table XI. The diagnosis of congenital short oesophagus, which is based almost exclusively on findings at operation, has not been made in the present series. The differences between the two series (Allison's shows a higher incidence of sliding hernia) are not entirely explained by surgical selection, but are partly indicative of the difficulties inherent in classification.

Symptoms. The present study confirms the view that there are two orders of symptoms in hiatus hernia: one associated with the hernia (flatulence, vague dyspepsia, vomiting, anaemia, and some forms of dysphagia), and the other associated with reflux oesophagitis due to an incompetent cardia. When symptoms are oesophageal rather than hernial, the hernia is of secondary importance, equally severe symptoms being met where gastro-oesophageal reflux is present without a hernia (Lawler and McCreath, 1951). The oesophageal symptoms are undoubtedly associated with inflammatory changes in the oesophageal mucosa (Allison, 1951), and clearly predominate in sliding and in most combined hiatus hernias.

Aetiology. It will be apparent that, with the exception of a small group of sliding hernias occurring in women during pregnancy, the disorder is one of middle and later life, the great majority of patients first seeking advice in the fifth to seventh decades. Degenerative factors may therefore play a part in the

aetiology. The general relaxation of ligaments and increase of fibrous and fatty tissue, particularly around the hiatus, combined with obesity and other causes of increased intra-abdominal pressure (pregnancy and gynaecological disorders in women), seem a sufficient explanation in most cases, and one which is in keeping with the observed facts. Branwood (1948) found obesity in 80 per cent. of cases, and felt that in women tight corsets were a factor. A congenital predisposition seems likely, especially in cases occurring earlier in life. Pregnancy is undoubtedly an important weakening and precipitating factor. Dutton and Bland (1953) described nine such cases and reviewed previous reports; Rennie, Land, and Park (1949) described five pregnant women who had dysphagia due to oesophageal stricture, secondary to hiatus hernia. In the present series 11 patients (10 with a sliding and one with a combined hernia) were seen in pregnancy (9 per cent. of the female S group). The experience reported here also indicates that, when a sliding hernia is found with either obesity or pregnancy, weight reduction or delivery may result not only in a loss of symptoms, but also in reversion to normal X-ray appearances. Duodenal ulcer and gall-bladder disorder have both been suspected as causes of hiatus hernia by vagal reflex. Cholecystitis and duodenal ulcer, however, are both common maladies in the absence of herniation, and the present study does not suggest any close association. In the case of rolling hernias, while degenerative factors explain the apparent onset of the condition in middle life, the size of the hiatal or parahiatal defect, combined with the presence of a peritoneal sac in front of the oesophagus, probably indicates a potential congenital defect. Bourne (1951, 1952) visualized the fundus and greater curvature of the stomach being aspirated into the thorax as a result of the difference between thoracic and abdominal pressure. In the present series obesity was noticeably less common, but kyphoscoliosis and inguinal hernia more frequent, in cases of rolling than in those of sliding hernia. Finally, no case of pregnancy was complicated by a rolling type of hernia. It is concluded that sliding hernia is largely a degenerative condition, precipitated and aggravated by obesity and increased intra-abdominal pressure, while rolling hernia, though usually manifesting itself in later life, is occasioned by a congenital abnormality, aggravated sometimes by spinal (and thus presumably diaphragmatic) deformity.

Complications. Anaemia in hiatus hernia has been well recognized for many years. Ritchey and Winsauer (1947) recorded 11 instances of secondary hypochromic anaemia in 41 cases of hernia. Effler and Ballinger (1951) found evidence of chronic blood loss in seven out of 16 cases of thoracic stomach with short oesophagus. Roussak and Eden (1947) described one case, also in a patient with a very large para-oesophageal hernia. Few writers, however, have stressed the fact that profound anaemia is almost always associated with a large hernia (either rolling or combined); yet the size of the hernia is clearly of importance. In the present series the anaemia has been of the hypochromic, iron-deficiency type, and frequently associated with occult blood in the stools. It seems reasonable to infer a state of chronic or intermittent mucosal venous congestion in the gastric pouch. Such a state of affairs would fit in with the observed facts

of anaemia, occasional haematemesis, and chronic gastric ulceration, for in some cases peptic ulceration may coexist in the abdominal portion of the stomach (Kaplan, 1951).

The oesophagitis which complicates hiatus hernia (especially the sliding and combined forms) is clearly related to the presence of irritating gastric juice in the oesophagus. The work of Aylwin (1953) suggests that this juice has been secreted in, and regurgitated from, the supradiaphragmatic pouch of stomach. He found a relationship between the degree of oesophagitis and the nocturnal peptic activity in the thoracic gastric pouch, and concluded that it is the acid secreted above the diaphragm which is most damaging. In cases of truly sliding hernia, in which the lesion is reducible and reflux only intermittent, oesophagitis is much less marked. The incidence of secondary oesophageal stenosis varies in different series. In a 10-year period Rennie, Land, and Park (1949) encountered 26 cases, compared with 80 cases of oesophageal carcinoma and 31 of achalasia. Stensrud (1954) described six cases of stricture in 31 cases of sliding hernia (20 per cent.), and Allison (1951) 63 cases of stenosis among 176 sliding hernias (36 per cent.: 23 per cent. of the women and 54 per cent. of the men). This is an exaggerated incidence, since such a condition will inevitably reach the hands of a surgeon sooner than an uncomplicated hiatus hernia. In the present series stricture occurred in 5 per cent. of the 'sliding' group (8 per cent. of the men and 4 per cent. of the women). Many surgeons aim to operate early on sliding hernia, in order to minimize regurgitation and the danger of oesophageal stricture. In the author's experience, however, strictures have always been found to be an established complication, often with a brief history of dysphagia simulating oesophageal carcinoma, and in no case has a patient under observation and treatment developed stenosis. Furthermore, patients with stricture rarely gave a history of reflux extending back over several years and preceding the onset of oesophageal symptoms. They were of normal build, without the obesity characteristic of patients with sliding hernias; and, finally, the hernia was often insignificant, and difficult to demonstrate below the stricture. It is concluded that peptic oesophageal stricture is a rare complication of hiatus hernia, and that when it does occur special factors are in operation. These include duodenal ulceration (two of the three men in this series), pregnancy (Rennie, Land, and Park, 1949), and some congenital abnormality such as true short oesophagus, or gastric ulceration in a portion of oesophagus lined by gastric mucosa (Barrett, 1950–1; Allison and Johnstone, 1953).

Episodes of acute pain in the chest due to hiatus hernia or oesophagitis may mimic the pain of cardiac infarction both in nature and in distribution. Von Bergmann (1932) demonstrated a fall in coronary blood-flow in dogs subjected to balloon distension of the oesophagus. It has been suggested that such a state of affairs may occur in man in the presence of hiatus hernia or oesophageal disease. Oesophageal pain, however, does not appear to produce cardiographic changes (Wolferth and Edeiken, 1942; Harrison, 1945), even when the oesophagus is distended by a balloon in the presence of known coronary artery disease (Baylis, Kauntze, and Trounce, 1955; Balint and Edmunds, 1955).

Patients suffering from hiatus hernia and angina can often distinguish between the two pains. Pain from hiatus hernia is rarely related to exertion, but rather to posture and the taking of food; dyspepsia often accompanies it, and regurgitation of acid or food may follow.

Treatment. Conservative measures are worth an extensive trial in uncomplicated cases of hiatus hernia. Edwards (1954) was of the opinion that rolling hernias should be treated surgically, because of the danger of the large gastric hernia becoming strangulated. Such a complication undoubtedly does rarely occur (Vorhaus and Stetten, 1944; Pearson, 1953; Sellors and Papp, 1955–6), but does not appear to be common enough to warrant advising a major surgical procedure to someone whose symptoms may be slight. Oral iron will control the anaemia. In those rare instances in which the hernia contains other viscera in addition to stomach, repair should be carried out. When resorted to, the object of surgery is the reduction of the hernia and the reconstitution of the hiatus so as to control any hiatal incompetence. This applies particularly to the sliding and combined types of hernia. Nevertheless, lesser measures, such as left phrenic crush, for the elderly or infirm (Pickhardt, Rafsky, and Ghiselin, 1950) and in infancy (Pettersson, 1952), and partial gastrectomy (Franklin, 1952), are often adequate. Repair may be either transthoracic (Sweet, 1948; Allison, 1951; Belsey, 1952*a*; and the present series) or abdominal (Harrington, 1948; Tanner, 1955). Both methods have their advantages. The former permits a good exposure of the hernia and the phreno-oesophageal ligaments, which can be divided and resutured below the diaphragm; the latter has the advantage that a laparotomy may be performed concurrently, any unsuspected gall-stones, ulcer, or more serious condition being dealt with at the same time.

For oesophageal stricture many surgeons are unhappy about resection followed by direct oesophago-gastrostomy, fearing the recurrence of stricture higher up the oesophagus. Allison (1951) advised resection followed by anastomosis with a loop of jejunum. Although the stomach is kept as a blind loop, this procedure virtually amounts to performing a total gastrectomy, which for a benign condition seems a drastic measure. Belsey (1952*b*) favoured resection of the stricture together with the fundus, upper half of the body of the stomach, and upper two-thirds of the lesser curvature. An end-to-end anastomosis is then performed between the oesophagus and the reconstructed stomach. This procedure was adopted in three patients of the present series with complete success. Belsey (1953) regarded the use of bougies in the same light as oesophago-gastrostomy: that is, as liable to encourage further reflux oesophagitis, and recurrent stenosis of the oesophagus possibly at a higher level. Kelly (1953), on the other hand, was satisfied with their use, providing medical measures were also adopted for oesophagitis. The small experience so far gained in the present series accords with the latter view.

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Summary

1. The nomenclature of hiatus hernia is reviewed.

2. A study is recorded of 200 cases discovered during the routine investigation of dyspepsia. One hiatus hernia was discovered in every 30 barium meals (3·3 per cent.), compared with one in 10 for gastric and one in 2·6 for duodenal ulcers.

3. The hernias have been classified as sliding (145), rolling (35), and combined (20). The incidence of the condition gave a female:male ratio of 4:1, the commonest lesion being the sliding in women and the rarest the rolling in men.

4. Apart from a small group of sliding hernias occurring in women during pregnancy, it is essentially a disorder of middle or later life, the majority of patients seeking advice in the fifth to seventh decades.

5. With sliding hiatus hernia the main complaints were epigastric pain, heartburn, regurgitation, vomiting, flatulence, haematemesis, and dysphagia. Gastro-oesophageal regurgitation was demonstrated in 93 per cent. of cases, and most of the symptoms with this type of hernia were oesophageal, arising as a direct result of incompetence of the cardia. Obesity was noticeable in 66 per cent., and pregnancy present in 9 per cent., of this group of patients.

6. With rolling hernia the main feature was anaemia. Iron-deficiency anaemia was found in 55 per cent. of cases. It seemed to be due to loss of blood, and responded to oral iron, a treatment which is continued indefinitely. Kyphoscoliosis was present in 60 per cent., and borborygmi were audible over the sternum in half of the patients. Symptoms were vague, being mainly those of flatulence or related to anaemia.

7. Combined hernia presented a composite picture and symptomatology.

8. The view that the majority of hiatus hernias are symptomless was not supported in this series. In 97 per cent. of the patients the hernia was the main source of dyspepsia. But the appearance of symptoms was occasionally related to an underlying gastric neoplasm or abdominal tumour.

9. Aetiological factors in sliding hiatus hernia seem to be a congenital predisposition or hiatal weakness, degenerative changes, and increased intra-abdominal pressure due to pregnancy, tumour, or obesity. In rolling hernia intra-abdominal pressure does not appear to be such an important factor, and the herniation depends on the presence of a preformed peritoneal sac and possibly diaphragmatic deformation by kyphoscoliosis.

10. The radiological examination of such cases is briefly outlined.

11. The complications met in this series were haematemesis, melaena,

anaemia, and oesophageal stricture. There were no instances of strangulation or perforation.

12. Medical measures, including weight reduction, small meals, the use of posture, and the administration of antacids and iron where appropriate, were generally successful. Some form of surgical treatment was resorted to in 33 cases. In 23 of these the hiatus was repaired by the transthoracic route; symptoms of reflux oesophagitis recurred after six months' freedom in five patients (21 per cent.). Of the remaining 10 patients, partial gastrectomy was performed in four, phrenic crush in one, resection of an oesophageal stricture in three, and dilatation of a stricture in a further two.

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FIG. 1 (*a*). Sliding hernia in pregnancy

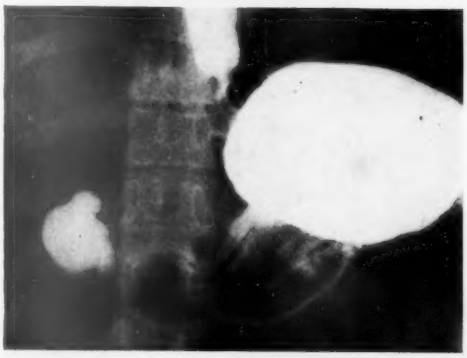


FIG. 1 (*b*). The same case after delivery, showing hernia reduced

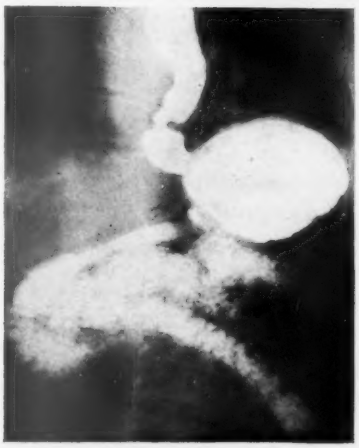
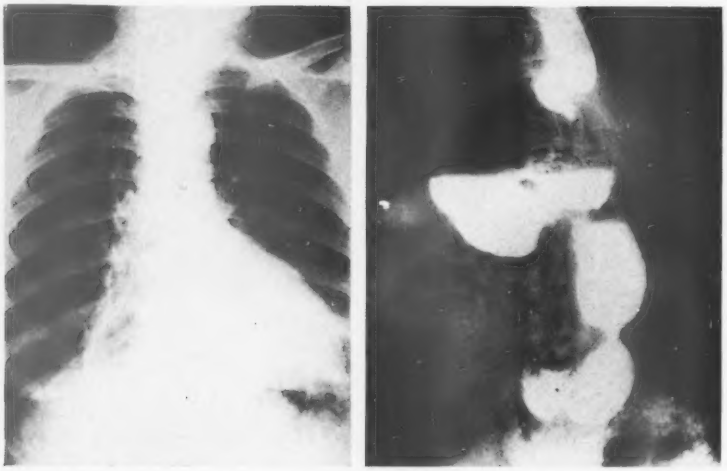


FIG. 2. Sliding hernia associated with an ovarian cyst which occupies the lower half of the abdomen. The oesophagus is not shortened but enters the apex of the hernia



a *b*

FIG. 3. Rolling hernia. (*a*) Plain X-ray of the chest, showing a cystic area to the right of the heart. (*b*) The same patient on barium examination

FIG. 4. Combined hernia. There is kyphoscoliosis

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DIABETIC DIARRHOEA[1]

By J. M. MALINS and J. M. FRENCH

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Diarrhoea of diabetes is a title first used by Bargen, Bollman, and Kepler (1936) when recording an intractable diarrhoea of undetermined aetiology in diabetic patients. The authors stated that they found no evidence of failure of the external secretion of the pancreas: symptomatic measures and commercial pancreatic extracts appeared to have no sustained effect. Sheridan and Bailey (1946) described 40 cases of a similar character in the Joslin Clinic. The typical symptom was intermittent nocturnal diarrhoea with brown watery stools, and nocturnal incontinence was common. Neuropathy was noted in 23 of the patients. Fifty-six additional cases were seen at the Joslin Clinic in the next five years (Joslin, Root, White, and Marble, 1952). Rundles (1945), in a detailed survey of diabetic neuropathy, pointed out the frequency of disturbances of the gastrointestinal tract in 125 cases; in 27 continuous or recurrent diarrhoea was a feature. Swarts and Stine (1948) described a patient in whom diabetes was complicated by visceral neuropathy, with alternating constipation and diarrhoea, and in more recent writings it has been customary to assume that persistent diarrhoea in diabetic patients is due to autonomic disturbances (Hodges, Rundles, and Hanelin, 1947; Sancetta, Ayres, and Scott, 1951; Joslin, Root, White, and Marble, 1952; Hirson, Feinmann, and Wade, 1953; Martin, 1953*a*; Goodman, Baumoel, Frankel, Marcus, and Wassermann, 1953; Brandon, 1954). Berge, Wollaeger, Scholz, Rooke, and Sprague (1956) have reported six cases of steatorrhoea complicating diabetes with neuropathy. In the absence of any evidence of other causes of steatorrhoea it was assumed that an autonomic disturbance, shown by decreased transit-time of food particles, a deficiency pattern on X-ray examination, and abnormalities of sweating, was primarily responsible. In two further patients with steatorrhoea, however, there was no evidence of neuropathy. The present paper records the clinical findings and the results of investigations in a series of cases of diabetic diarrhoea.

Patients Investigated

The 28 patients with diabetes mellitus were selected from the Diabetic Clinic at the General Hospital, Birmingham, because they had long-standing symptoms akin to those already described as characteristic of diabetic diarrhoea. Seventeen were men and 11 women, and 22 had been receiving insulin for at least one

[1] Received December 6, 1956.

year before the onset of diarrhoea. The other six had a constantly raised blood-sugar level when the diarrhoea was first noted, and later needed substantial doses of insulin. The diarrhoea was observed for a period ranging from one to 19 years, and in no case was any cause for it established other than diabetes. The average age at the onset of diabetes was 35 years (range 14 to 68) and at the onset of diarrhoea 42·3 years (range 22 to 72) (see Table).

Clinical Picture

The complaint was of bouts of diarrhoea, usually of considerable severity, with frequent watery or very loose stools of big volume. In 10 of our 28 cases the diarrhoea was troublesome only at night, and when this was so there might be faecal incontinence. Pain was unusual, and was mostly described as a feeling of discomfort in the lower abdomen. Some attacks continued with great intensity for a few days, subsiding spontaneously, with very little disturbance of the general health. On one occasion one man reported that 'he had not been able to get his trousers on once for over 48 hours', yet the following day he passed no stool, appeared perfectly well, and was at work. The diarrhoea was characteristically intermittent. In mild cases an occasional episode of a day or two interrupted many weeks of normal bowel action. In the most severe cases attacks of diarrhoea, continuous for months, might be interrupted by a spell of normal habit or even constipation, which made the result of treatment difficult to evaluate. The course and the degree of disability were most variable. One patient (Case 8) became subject to brief bouts of nocturnal diarrhoea four years after the onset of severe diabetes, and is still troubled occasionally by them 22 years later. Another (Case 10) has had attacks for 28 years, continuous and intractable for the last seven years, but is still able to carry on heavy housework. In Case 11 diarrhoea has been so severe that this symptom alone has prevented the patient from working more than 18 months out of the last 10 years. Factors predisposing to attacks of diarrhoea were not apparent. No patient reported that the character of the diet had any influence on the frequency of the stools, or that an attack could be attributed to indiscretion in eating. Only one considered that emotional stress played any part in precipitating symptoms, nor was there evidence in our patients of deviation from the normal personality found among a diabetic population. Of the three women still menstruating, one reported no relation of the diarrhoea to the menses; one had attacks rather constantly in the week before a period, and one in the week following a period.

Duration of Diabetes

The date of onset of diabetes is usually difficult to define, and in certain cases in the present series there is reason to believe that the condition had been present for years without symptoms. The date of onset was taken to be the time when classical symptoms of diabetes began, or when glycosuria was discovered if no such symptoms occurred. In 27 patients the duration of the

diabetes at the onset of diarrhoea was 0 to five years in seven, five to 10 years in 15, and more than 10 years in five (see Table).

The State of Diabetic Control

The control of diabetes, for two years before the onset of diarrhoea, was judged to be poor in 15 patients and moderate in 13. No patient was considered well controlled. Those with poor control had constant symptoms of diabetes, invariable glycosuria, and an average blood-sugar level atfer the midday meal exceeding 300 mg. per 100 ml. The remainder, with moderate control, had only occasional diabetic symptoms, the fasting specimen of urine was sometimes free of sugar, and the average level of blood-sugar after the midday meal was 200 to 300 mg. per 100 ml. Once diarrhoea had developed, short periods of good or bad control had no consistent effect on the diarrhoea, though prolonged episodes (one month or more) of poor control were associated with relapse in five cases. Of the 16 patients who achieved good control for one year or longer, only three were permanently relieved of diarrhoea.

Clinical Findings

The body-weight at the onset of diarrhoea was normal for height and age in 22 patients (Kemsley, 1951–2). In three it was more than one stone below the average, and in two it was more than one stone above. There was no evidence of heart disease, and no patient gave a history of coronary occlusion or of anginal pain. Retinopathy was found in two patients at the onset of diarrhoea—a man known to have had diabetes for 15 years, and a woman whose advanced retinopathy was found at the first discovery of glycosuria. Albuminuria was found in one case at or near the onset of diarrhoea; but at the end of the period of observation nine patients had constant albuminuria, which in four was associated with other features suggestive of the renal disorder described by Kimmelstiel and Wilson (1936).

Neuropathy. Unequivocal evidence of peripheral neuritis was found in 16 patients, who complained of night cramps and paraesthesiae; knee- and ankle-jerks were absent, and vibration sense at the ankle was lost. In another four patients there were suggestive symptoms, but no abnormal physical signs. In seven the characteristic diarrhoea was observed for periods of one to 10 years without other clinical evidence of peripheral neuritis. There was also evidence of autonomic nerve involvement. Ten of the 17 men were impotent at the onset of diarrhoea, and two had been troubled by precipitate micturition. Nine of 12 patients examined for disordered sweating showed extensive areas in which sweating did not occur on raising the body temperature. Fourteen gave a history of night sweats not attributable to hypoglycaemia. Orthostatic hypotension was found in three patients who gave a history of faintness on rising from bed.

The stools. In all cases the stools were brown in colour, unlike the pale stools typical of the sprue syndrome; usually homogeneous and of a thin, soup-like

Clinical Features in 28 Cases of Diabetic Diarrhoea

Patient	Sex	Age at onset of diabetes	Age at onset of diarrhoea	Diarrhoea observed (years)	Control of diabetes before diagnosis	Control of diabetes after diagnosis	Neuropathy Degree	Neuropathy Manifestation	Result
1. N. S.	M	14	22	8	Moderate	Good	+	P	Occasional diarrhoea
2. J. G.	M	19	25	6	Poor	Good	0	—	Occasional diarrhoea
3. D. T.	M	19	25	10(D)	Poor	Moderate	+	R; A; U; S; I; O	Died. Diabetic nephropathy
4. H. H.	F	18	26	5	Moderate	Good	0	—	Occasional diarrhoea
5. M. E.	F	20	29	4	Moderate	Good	+	P	Occasional diarrhoea
6. J. M.	M	29	34	6	Poor	Good	++	P; R; A; S; I	Occasional diarrhoea
7. I. B.	M	31	34	2(D)	Poor	Poor	+	P; R; A; S; I	Died. Acute pyelonephritis
8. E. B.	M	29	34	19	Moderate	Good	+	R; A	No diarrhoea
9. M. L.	M	30	35	11	Poor	Good	++	P; R; A; S; I	Frequent diarrhoea
10. F. R.	F	16	35	16	Moderate	Good	+	R; A	Frequent diarrhoea
11. W. G.	M	28	35	11	Poor	Poor	++	P; R; A; S; I; O	Frequent diarrhoea
12. K. T.	F	36	36	10	Nil	Good	0	—	No diarrhoea
13. G. H.	M	32	39	5	Poor	Good	++	P; R; A; U; S	Occasional diarrhoea
14. J. L.	M	39	40	12	Moderate	Moderate	+	P	Occasional diarrhoea
15. J. H.	M	35	40	14(D)	Poor	Poor	+	P; R; A; S; I	Died. Acute pyelonephritis
16. T. P.	M	32	41	6	Moderate	Good	+	R; A; S; I	Occasional diarrhoea
17. H. S.	M	42	42	1(D)	Nil	Good	+	P; R; A; U	Died. Hypoglycaemia
18. F. A.	F	35	43	5	Moderate	Moderate	0	—	Occasional diarrhoea
19. F. C.	M	35	45	3	Poor	Moderate	++	P; S; I	Frequent diarrhoea
20. A. J.	M	45	48	5	Moderate	Moderate	0	—	No diarrhoea
21. J. W.	M	35	50	2	Poor	Poor	+	P; R; A; S; I	Nephrotic syndrome
22. J. C.	M	50	51	11	Poor	Good	++	P; R; S; I	Occasional diarrhoea
23. L. M.	F	45	54	15	Moderate	Moderate	+	R; A	Occasional diarrhoea
24. E. H.	F	30	59	3	Moderate	Good	++	P; R; A; S	Occasional diarrhoea
25. D. N.	F	?	62	7	Nil	Good	++	P; R; A; S; I; O	Frequent diarrhoea
26. M. P.	F	60	65	8	Moderate	Good	0	—	Occasional diarrhoea
27. L. A.	F	50	61	1	Moderate	Moderate	0	—	Occasional diarrhoea
28 R. H.	F	68	72	3	Poor	Good	+	P; R; A; S	Occasional diarrhoea

P = neuritic pain. R = absent knee and ankle jerks. A = patchy anaesthesia.
U = perforating ulcer. S = disorder of sweating. I = impotence. O = orthostatic hypotension.

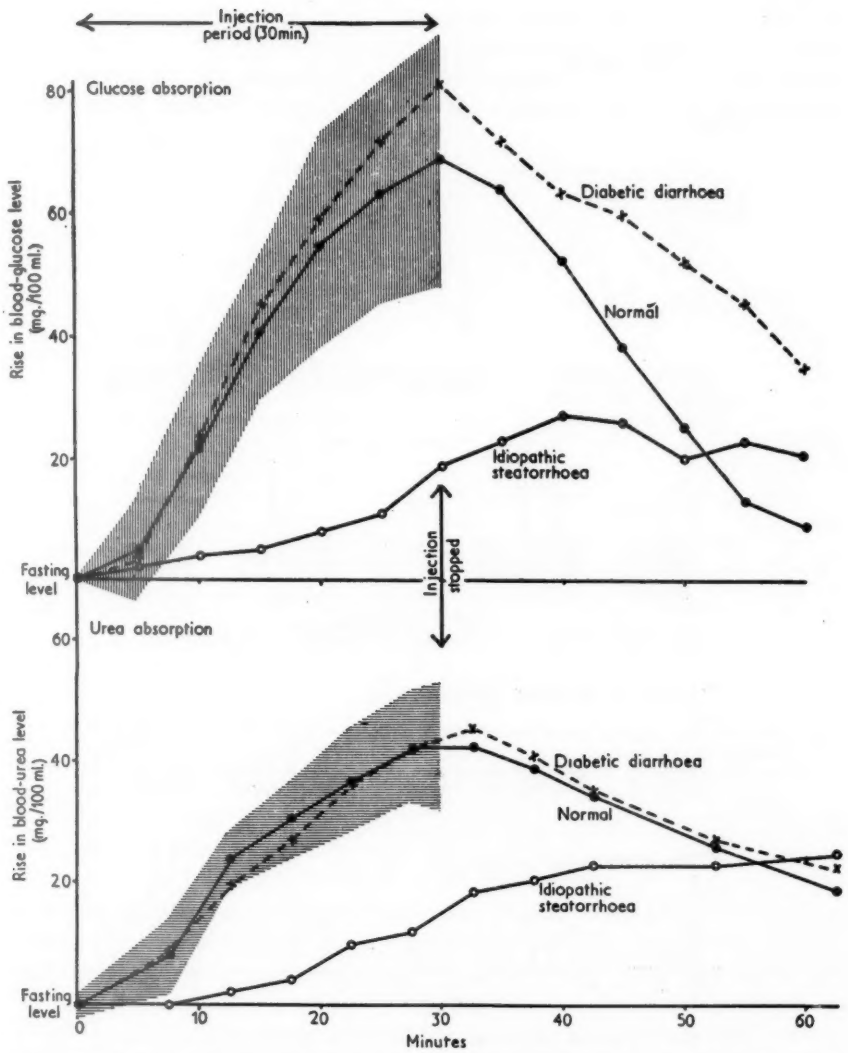

FIG. 1. Intraduodenal glucose and urea absorption. Fifteen gm. of glucose and 15 gm. of urea in 300 ml. of water were injected into the duodenum (10 ml. per minute) over a period of 30 minutes. Simultaneous estimations of blood-sugar and blood-urea were made over a period of one hour. The mean rise from fasting level in a group of five cases of diabetic diarrhoea is compared with that found in five normal subjects and 10 patients with idiopathic steatorrhoea. In diabetic diarrhoea the rate of absorption in the upper intestine during the injection period fell well within the limits of twice the standard deviation of the normal mean (shaded areas), quite unlike that found in idiopathic steatorrhoea.

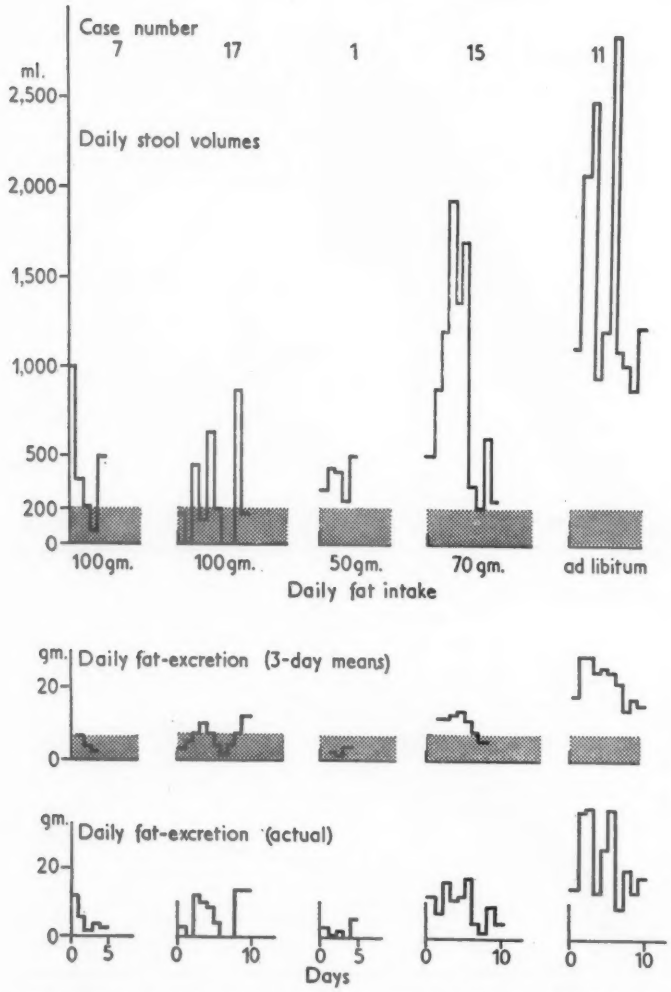

FIG. 2. Daily faecal volumes and fat-excretion in five cases of diabetic diarrhoea. In the first three patients moderate diarrhoea was associated with a normal fat-excretion. In the other two, more profuse diarrhoea was associated with mild steatorrhoea in one case and gross steatorrhoea in the other. The shaded area for fat-excretion shows the approximate upper limit of normal. The shaded area for faecal volume is an approximate level at which looseness of the stools commonly became apparent. Pancreatic enzymes were normal in all five patients.

consistency, they were at times very watery, in which case undigested vegetable debris was easily recognizable. The general appearance resembled that of ileostomy fluid. The microscopic appearances studied in detail in five cases were as follows. (1) *Meat-fibres* were seen in profusion in both an undigested and a partly digested state. (2) *Starch*. Many intracellular potato-starch cells

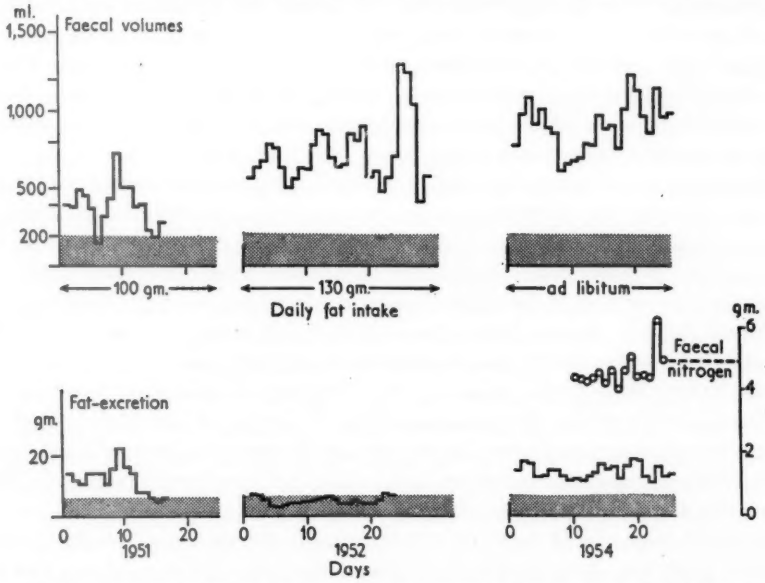

FIG. 3. Average daily faecal volumes and fat-excretion in a patient with diabetic diarrhoea (Case 11) at different periods. In 1951 diarrhoea and excessive faecal volumes were associated with definite steatorrhoea. In 1952 the diarrhoea was increased but the steatorrhoea less. In 1954 the diarrhoea was slightly worse, and gross steatorrhoea was again present. Faecal nitrogen loss was estimated during the third period, and was also found to be excessive (normal upper limit about 2·0 gm.). Three-day mean values for volume, fat, and nitrogen are shown for periods of two to three weeks.

were seen on numerous occasions in all cases. Naked starch granules, however, were seen consistently in large numbers in only one case. (3) *Fat* was seen in two cases in the form of unemulsified globules, some surrounded by fatty-acid crystals, like a rosette. These rosettes represent poorly emulsified fat in a state of partial hydrolysis, and are thought to indicate intestinal hurry (Goiffon, 1952); they were most frequently seen in the watery stools. (4) *Iodophilic bacteria*. Staining of the stools for starch with iodine frequently resulted in a deep-violet colour, with no excess of visible starch granules. If the faeces were boiled, cooled, and filtered, addition of iodine to the filtrate showed no iodine reaction, whereas the solid residue stained deeply: it was found that this was due to a great excess of iodophilic bacteria (*Clostridium aceto-butylicum*), which are normally present in quantity only in the upper colon or lower ileum (Goiffon, 1949).

Pancreatic enzymes (five cases). In each case two or more samples of alkaline

clear yellow juice were aspirated from the duodenum under radiological control. The levels of amylase, lipase, and trypsin were normal in all cases except one, in which the amylase only was somewhat diminished, lipase and trypsin being normal. There was, therefore, no evidence of a deficiency of external pancreatic secretion.

Absorption from the upper intestine (five cases) was measured by a study of blood-glucose and blood-urea levels after the gradual intraduodenal administration, over a period of 30 minutes, of 300 ml. of a solution containing 15 gm. of glucose and 15 gm. of urea (Frazer, French, Thomas, and Thompson, 1952). A rapid increase of blood-sugar and blood-urea, equivalent to that seen in normal subjects, occurred in all five cases examined (Fig. 1).

Systemic post-absorptive lipaemia (five cases). One ounce of butter, containing 24 gm. of butter-fat, with bread and a cup of tea, was given to the patient fasting, and during the next five hours the systemic lipaemia was studied by the chylomicrograph technique. Subnormal rises in the chylomicron count in the systemic blood were seen in four of the five cases; the fifth showed a low normal rise.

Faecal fat (six cases). Estimation over several weeks, on diets containing 50 gm. and 100 gm. of fat, showed that the faecal fatty acid was within normal limits in four cases (three shown in Fig. 2) during the period of examination. In two cases an excess of fat was seen (Fig. 2). Study of one of these patients over prolonged periods showed steatorrhea to be severe in 1951, almost absent in spite of continued and increased diarrhoea in 1952, and again present in 1954, when the diarrhoea had become still worse (Fig. 3).

X-ray findings. In 12 patients a barium enema gave a normal result. In 14 a barium meal was given with follow-through films for 24 hours, and in five the examination was carried out with both flocculable and non-flocculating suspensions of barium sulphate (Ardran, French, and Mucklow, 1950). Of the 14 ordinary barium meals five showed some delay in gastric emptying, more than one-third of the meal still being in the stomach at the end of four hours. Transit through the small and large intestine was generally rapid, and in no case slow, the caecum being reached within 15 minutes and the sigmoid colon in six hours in every patient. The interpretation of the rate of the passage of barium is difficult, as the character of food, especially fat, may greatly influence the rate of intestinal transit (Menville and Ané, 1932; Reynolds, Macy, Hunscher, and Olson, 1940). In one case barium sulphate was given with a normal mixed breakfast, but the result was the same as with the barium alone, complete gastric emptying being delayed for 12 hours, with the head of the meal at the sigmoid in four hours. In no case was there a significant difference between the patterns observed with flocculating and non-flocculating barium sulphate, and there was no sign of excessive mucus secretion in the small intestine.

Sigmoidoscopy. The colon was examined to 20 cm. in eight patients, and was normal.

Fractional test meal. Nine of 13 patients had normal acidity; four had histamine-fast achlorhydria. There were no other unusual features in these four patients.

Liver function tests were performed on the serum in 14 patients, and included estimations of bilirubin, albumin and globulin, and alkaline phosphatase, with the colloidal gold and thymol turbidity reactions. Normal results were obtained in every case.

Treatment

Diabetic control. Whatever the cause of the diarrhoea, it seemed reasonable to make strenuous efforts to maintain good control of the diabetes. In 10 of our patients control, which had been poor or moderate, became excellent for at least two years; but the diarrhoea was unchanged in six cases, while in four it improved but did not disappear. Martin (1953*a*) found that half of his patients with diarrhoea recovered with good control of the diabetes.

Diets. Change to a low-residue diet for a short period did not appear to have any effect, and was not considered worth pursuing, in view of the difficulty of devising such a diet for a diabetic patient. Diets with low fat and high carbohydrate content, with high protein and low carbohydrate content, and with low fat and low carbohydrate content were given for limited periods (two to three weeks) to patients in hospital, but without significant improvement.

Drugs. Mixtures containing chalk, opium, bismuth, or codeine were without significant effect in checking the diarrhoea. Liver extract was regarded by Sheridan and Bailey (1946) as of value in this condition. Between 1946 and 1950 liver extract was used by one of us (J. M. M.) in 11 patients. The diarrhoea improved at once in eight cases, but relapsed in three while the injections were continued, and in the other five when the injections were stopped. In the remaining three patients diarrhoea was unaffected. In 1950 it was observed that folic acid had a similar effect. Cyanocobalamin (100 μg. weekly by injection for three months) was given to two patients with diarrhoea of average severity, without effect. In 1951 one of the patients, with a coincidental urinary infection, was treated with chlortetracycline. Her diabetic diarrhoea, which was then very severe, was immediately relieved. Chloramphenicol, used in one case, had a similar effect in stopping the diarrhoea. Since that time chlortetracycline has been given to 22 patients with this condition. In 16 cases the diarrhoea has been controlled completely; in five, the most severe, there was no improvement, and two of the latter patients have since died. The dosage originally used was 250 mg. thrice daily but we have since found that a single capsule of 250 mg. often has a prolonged effect. Thus, in patients with continuous or prolonged attacks, the condition may be controlled by one dose daily, while those with less frequent attacks have found it sufficient to take one dose at the onset of symptoms. Three of the patients, who previously had nocturnal incontinence, have maintained control with one capsule of 250 mg. weekly. One reported that two capsules in a day led to constipation, whereas one did not wholly prevent diarrhoea. Five have emphasized the immediate effect of taking a capsule; within half an hour the abdominal discomfort with borborygmi, which commonly preceded an attack, subsided completely. A practical advantage of this therapy

is that it can be used only as the need arises, and does away with the necessity for continuous treatment in patients whose attacks are only occasional.

Course and Prognosis

The 28 patients in the present series have been observed for periods of two to 19 years. Eighteen of them have no serious disability, comprising 15 whose diarrhoea is relieved by chlortetracycline and three in whom the diarrhoea has ceased spontaneously. Four have frequent attacks, but only one of these four patients fails to respond to chlortetracycline, and is therefore an invalid. Two have a nephrotic syndrome with retinopathy, and are slowly deteriorating, but the diarrhoea is now rarely troublesome. Four have died. One (Case 7) died from ketosis with acute pyelonephritis in another hospital. Another patient (Case 15) drifted into a state of chronic malnutrition, in spite of good control of his diabetes, and died ultimately from a fulminating pyelonephritis. Post-mortem examination showed no other abnormality, and the histological appearances of the lumbar sympathetic and presacral nerves (with haematoxylin and eosin) were normal. A third patient (Case 17) was found unconscious in his flat, and died of irreversible hypoglycaemia. Post-mortem examination revealed no abnormality other than the changes in the brain. These three patients had failed to respond to any form of treatment for the diarrhoea. A fourth patient (Case 3) died at home of uraemia, with a nephrotic syndrome clinically typical of diabetic nephropathy.

It appears that long-continued diarrhoea is not necessarily associated with a high incidence of other diabetic complications, as four of the 10 patients who suffered from diarrhoea for 10 years or more were without other symptoms. The effect of proper control of diabetes on the prognosis is not easy to assess in such a small series, but, of the four patients in whom control remained poor at all times, diarrhoea was a contributing factor in the death of two (Cases 7 and 15), one still has severe diarrhoea, and one has a nephrotic syndrome.

Discussion

The cause of the diarrhoea. Malabsorption, as seen in the sprue syndrome, cannot be the basis of the diarrhoea. There was no flattening of the absorption curves after the intraduodenal administration of glucose and urea (Fig. 1), and the faecal fat, although sometimes in excess, was sometimes normal in amount when the stools were large in volume (Figs. 2 and 3). This finding suggests that the diarrhoea is due to rapid passage through the colon. The increase in fluidity and volume of the stools must mean either that the bowel empties before the normal colonic dehydration has taken place, or that there is an excessive volume of water to be absorbed, or that there is an excessive colonic secretion. The X-ray evidence, and the presence of undigested vegetable material, favour a rapid emptying of the colon as the explanation. The microscopic appearances, however, indicated that passage through the small intestine might also be

accelerated. Large numbers of meat-fibres were seen, sometimes discrete, but often in sheaves, and there was at times much starch, especially potato starch. Partly emulsified fat was also frequently seen, even on occasions when the total amount of faecal fat was normal or just in excess of normal. The microscopic features indicated a lack of digestion, yet examination of the pancreatic secretion by duodenal aspiration showed the pancreatic enzyme levels to be normal, as other observers have found. It seems unlikely that, when fasting levels were normal, pancreatic secretion should have failed during the passage of a meal. The defect in fat-absorption was relatively slight and intermittent in several of our patients, quite unlike that seen in cases of true insufficiency, such as we have found in pancreatic lithiasis, chronic pancreatitis, and pancreatic atrophy. It is difficult to escape the conclusion that some portion of the food was passing through the upper part of the intestinal tract too fast for adequate mixing with the pancreatic juices, and arriving in the colon in a state of very limited digestion. The increase in vegetable matter and the iodophilic flora also indicated rapid passage through the colon.

Barium-meal examination for evidence of increased speed of transit was inconclusive. In most cases the caecum was reached by the head of the meal in 15 minutes, which is rather fast, but much of the meal remained in the stomach for longer than normal. Although the times were not entirely normal, the range of normal is so wide that no clear indication was given as to what occurred to the bulk of the meal. In any case such a meal is only an index of the passage of inert barium sulphate, and cannot provide exact information as to what happens to a meal containing food; in one case, in which barium sulphate was added to breakfast, the times observed were about the same as without the food. The intestinal pattern was normal with both types of barium, a finding which is quite different from that obtained in the sprue syndrome. Radiological examinations by other observers support these findings in the main, though there are some differences. Rundles (1945), in four cases, reported some degree of gastric retention, slow transit through the jejunum and ileum, and segmentation, though in one case transit was rapid; Giansiracusa (1953) observed one case in which barium travelled from mouth to anus very rapidly (20 minutes). Swarts and Stine (1948), in a patient who had gross neuropathy with urinary retention and occasional diarrhoea, showed delayed emptying of the stomach and segmentation in the small intestine. Berge, Wollaeger, Scholz, Rooke, and Sprague (1956) found a deficiency pattern with steatorrhoea in two of their patients; in four others the pattern was normal, but there was increased speed of passage through the intestine. Sheridan and Bailey (1946) reported a normal barium series in 17 examinations, and Martin (1953*a*) reported 14 patients with diarrhoea in whom the result of the barium meal was normal except that nine showed gastric delay.

Diarrhoea with radiological evidence of gastric delay is seen after vagotomy (Priviteri, 1951), and by analogy this fact suggests that in diabetic diarrhoea the alterations in intestinal motility might be due to autonomic nerve degeneration. Observation in experimental animals has shown that diarrhoea associated

with disturbance of intestinal co-ordination may occur with section and degeneration of either parasympathetic or sympathetic nerves, and death of the animals often ensues (Alvarez, 1948). Although the results are rather unpredictable, one consistent finding in both man and experimental animals is the loss of tone and delay in complete emptying of the stomach which result from vagotomy. After splanchnicotomy (in dogs) the time of initial evacuation is also shortened, with permanent upset of the normal duodeno-pyloric reflex evoked by acids and fats (Cerqua, 1935). A study of 300 patients after bilateral sympathectomy for hypertension showed that 18 per cent. had increased bowel actions, and two per cent. had persistent and distressing diarrhoea (Bingham, Ingelfinger, and Smithwick, 1950). The disturbances after nerve section with degeneration resemble those disclosed by radiological studies in diabetic neuropathy, lending support to the idea of a degenerative condition of the autonomic nerve-supply of the gastrointestinal tract in diabetic diarrhoea, especially when there is evidence of autonomic nerve disorder in other parts of the body. Post-mortem examination in one of our cases, however, failed to show histological evidence of autonomic nerve degeneration, though Rundles (1945) was able to demonstrate it in two cases, and histological studies by Martin (1953*b*) led him to believe that the non-medullated nerve-fibres subserving the autonomic vasomotor and visceral responses were involved early in diabetic neuropathy. If there were derangement of the autonomic nerve-supply, the resultant incoordination of gastrointestinal motility might well be more noticeable when many of the central inhibitory influences were cut off during sleep, and so account for the predisposition of the diarrhoea to occur at night, and for the faecal incontinence which commonly occurs during sleep.

It is probable that autonomic nerve degeneration would result in a loss of balance in the normal stimulatory and inhibitory mechanisms; acetylcholine, and drugs which potentiate or prolong its action, such as neostigmine, are well known to stimulate colonic evacuation, and direct observations of the small and large gut during intravenous infusion of adrenaline have shown it to have a strong inhibitory influence in human subjects (Youmans, Haney, Rush, and Zavin, 1941). Trials of drugs along these lines were made in several cases. Neostigmine was found to make the diarrhoea worse; atropine, hexamethonium, banthine, and probanthine had no appreciable effect, although pressed to a level when interference with vision and bladder function were noted; and ephedrine, although it seemed temporarily to diminish the diarrhoea in one case, failed completely in a second.

The success of liver therapy recorded by Sheridan and Bailey (1946) suggests some deficiency as being responsible for the diarrhoea. They claimed that 26 of 28 patients were relieved, although a later survey of these patients (Joslin, Root, White, Marble, and Bailey, 1947) showed that only two of them were permanently relieved. Liver extract contains several of the B-vitamin fractions, of which cyanocobalamin is probably the most important. Although liver extract caused some remission in eight of our cases, relapse occurred during treatment in three, and in the remainder on cessation of treatment. Cyanoco-

balamin, entirely ineffective in two of our patients, has also been used in diabetic neuropathy by Sancetta, Ayres, and Scott (1951). Of patients who had gastro-intestinal symptoms they found that one, with diarrhoea, was unaffected. The effect of liver in diarrhoea does not, therefore, seem to be due to the cyanocobalamin fraction. Folic acid, partially effective in some of our patients, is present in very small amounts in present-day liver extracts, though the earlier crude extracts contained more. It is possible, therefore, that liver extract owes such effect as it has to the folic acid content. Estimation of serum folic acid (and cyanocobalamin) levels is needed before the temporary response can be attributed to rectification of a true deficiency.

Antibiotics. The remarkable effect of antibiotics in controlling the attacks of diarrhoea strongly suggests that the intestinal flora are in some way involved. It is apparent that if the antibiotic is withheld diarrhoea may return at any time—almost immediately in patients in whom it has been persistent. This occurrence suggests that the conditions primarily responsible for the diarrhoea (such as autonomic nerve degeneration) are still present, but that the antibiotic effect modifies the process. The arrival of undigested food in the colon may lead to a development of an unusual colonic flora, which in turn provokes precipitate emptying, or more probably the colon is abnormally sensitive to the usual colonic flora and their products. Control of the organisms with antibiotics establishes a less irritant content, and leads to cessation of the diarrhoea. A striking clinical feature in some cases of this disorder has been the maintenance of good nutrition even after years of diarrhoea, and this is consistent with the view, confirmed by analysis of the stools, that only a small proportion of the daily intake is precipitated with undue haste into the colon.

We wish to thank Dr. R. Gaddie, Mr. Garfield Thomas, and Mrs. Nadya Smith for assistance with the biochemical investigations. We are indebted to the United Birmingham Hospitals Endowment Research Fund, the Mackenzie Mackinnon Trust, and the Medical Research Council for financial help.

Summary

Twenty-eight patients with diabetic diarrhoea are described, together with investigations of the condition and its treatment. Steatorrhoea was present in two of five cases investigated by fat-balance studies.

Studies confirmed the presence of normal external pancreatic secretion, and malabsorption, as found in the sprue syndrome, did not appear to be present. A mechanism of small- and large-intestinal hurry, due to autonomic nerve degeneration, is inferred.

Improvement with liver extract and folic acid was observed in a number of patients, but the improvement was not maintained. Oral administration of chlortetracycline was effective in controlling the diarrhoea in 16 of the 22 patients in whom it was tried.

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THE EFFECT OF A WHEAT-GLUTEN-FREE DIET IN ADULT IDIOPATHIC STEATORRHOEA[1]

A Study of 22 Cases

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It is well established that coeliac disease in children is related to the consumption of wheat or rye flour. Treatment with a diet from which the glutens of both these cereals have been rigidly excluded results in recovery in almost every case (Dicke, 1950; Weijers and van de Kamer, 1950; Anderson, Frazer, French, Gerrard, Sammons, and Smellie, 1952; Sheldon and Lawson, 1952; Dicke, Weijers, and van de Kamer, 1953). Many cases of idiopathic steatorrhoea probably originate from coeliac disease in childhood. Thaysen (1932) found that approximately half of his patients had a history of acute or chronic intestinal disease in infancy or childhood; similarly Cooke, Peeney, and Hawkins (1953) found a definite or presumptive story of coeliac disease in 43 of 100 cases analysed. It would be logical to assume that the treatment of the adult disease would also be successful, at least in patients with such a history. Yet, hitherto, the treatment of this illness with a gluten-free diet seems to have been disappointing, and very few reports of success in adults have appeared since the original work of Dicke (1950) on coeliac disease. McIver (1952) and Haex and Lips (1955) each reported one patient who made a great improvement after the failure of cortisone therapy; Grytting (1954) reported improvement in one patient, and Ruffin, Carter, Johnston, and Baylin (1954) reported recovery in one and improvement in a further two patients; Schwartz, Pert, Roberts, and Randall (1956) reported remission in six cases, in two of which biochemical reassessment showed improvement in fat-absorption (also observed by Haex and Lips in their patient). Swan (1952) reported work with a gluten-free diet, and the addition of gluten under controlled conditions for short periods, in six cases, and came to the conclusion that wheat gluten played no part in the causation of the disease in adults. The object of the present report is to record the findings in 22 adult patients with idiopathic steatorrhoea who have been treated for a reasonable period of time with a diet from which wheat and rye glutens were excluded. It was found that complete recovery ensued in 16 patients, indicating the close analogy between the disease in children and that in adults. In the remaining six patients recovery did not occur.

[1] Received December 17, 1956.

Patients Studied and Methods

The series comprised 22 patients suffering from idiopathic steatorrhoea (non-tropical sprue). The history was characteristic in that they complained of years of ill health with the following symptoms: flatulence, with persistent loose, usually pale, stools, sore mouth and tongue, loss of weight, diminished appetite, and loss of energy. Sometimes other symptoms, such as tetany, were also present. Physical examination usually revealed some degree of malnutrition, which was gross in several cases; the abdomen was frequently distended; episodes of glossitis and stomatitis were observed in most cases, but not in all; cheilosis was seen less often. Apart from these findings there were no signs of disease other than those attributable to the malnutrition associated with the illness. Sigmoidoscopy was carried out in many patients, and showed no sign of organic disease of the rectum or sigmoid, the mucous membrance being at most hyperaemic. The clinical diagnosis was confirmed in all cases by the following special investigations: (1) *Fat-absorption* was measured with a controlled fat intake (usually 50 gm. daily), faecal fat being estimated by a modification of the method of van de Kamer, Huinink, and Weijers (1949): fat-excretion was abnormal (see Figs. 1 to 9), that is, more than 5 gm. per day, in all cases, the calculated fat-absorption being below 90 per cent. (2) *Duodenal intubation* was carried out under radiological control with a radio-opaque tube, and juice aspirated from the second or third part of the duodenum at intervals of a few minutes, without stimulation of pancreatic secretion by mecholyl or secretin. Only those specimens which were yellow, clear, and of a pH greater than 6·0 were used for the estimation of amylase, lipase, and trypsin, which were found to be present in normal concentration. (3) *Glucose-tolerance* tests, using an oral dose of 50 gm. glucose, were performed. There was a delayed and diminished rise in the blood-sugar level in nearly all cases. (4) *Blood examination* showed anaemia, which was macrocytic or hypochromic. Some of the patients showed both macrocytosis and hypochromia. Bone-marrow smears were made in several cases, and in two instances megaloblasts were seen. (5) *Radiological examination* of the gastro-intestinal tract was made with ordinary and non-flocculating suspensions of barium sulphate. No organic disease of the stomach or duodenum was seen; but, with ordinary suspensions of barium, flocculation occurred in the small intestine. Repetition of the meal with a non-flocculating preparation ('raybar') showed pictures varying from dilatation in the milder cases to a widely dilated 'ladder' pattern in the more severe (Ardran, French, and Mucklow, 1950).

The diet. All wheat and rye gluten was rigidly excluded from the diet. This meant that ordinary bread, pastries, cakes, biscuits, puddings, and gravies and soups thickened with wheat flour were not allowed. Special bread was made with wheat starch, and biscuits, cakes, pastries, &c., were made to recipes using wheat starch, maize, or rice flour, cornflour (maize starch), soya bean meal, or potato flour as substitute. Apart from the total exclusion of the wheat and rye glutens the diet was restricted as to fat intake only while the faecal output of fat was being measured. Some details of the diet have been published previously

(Hawkins, 1955). Strict control of additions made to the diet by patients' relatives was found to be essential.

Drugs. The ill state of the patients in some instances necessitated the use of certain drugs to alleviate symptoms or improve electrolyte and fluid balances. Thus kaolin, calcium salts, chalk and opium, and codeine were at times used to

TABLE I

Adult Idiopathic Steatorrhoea: Recoveries with Gluten-free Diet

Patient	*Age (years)*	*Sex*	*Duration of illness (years)*	*Any evidence of coeliac disease*	*Type of anaemia*	*Time before fat-absorption became normal (days)*	*Relapse induced by gluten or wheat flour*	*Recovery maintained (time in years)*
Recovery including normal fat-absorption:								
1. B. B.	21	F	?	Infantilism	Hypochromic	24 (Fig. 1)	Yes, wheat flour	4½
2. P. A.	29	F	8	No	Hypochromic	*c.* 200 (Fig. 5)	Yes, gluten	2
3. C. W.	33	F	14	Yes, at 5 and 19 years	Macrocytic	*c.* 90	No	3
4. L. S.	39	F	5	Small stature	Hypochromic	25	Yes, wheat flour	4½
5. K. S.	39	F	21	Small stature	Macrocytic	24 (Fig. 6)	No	3½
6. R. N.	39	F	15	'Pot-belly' in childhood	Hypochromic	*c.* 90	No	4
7. A. S.	40	M	15	No	Macrocytic	112 (Fig. 3)	Yes, wheat flour and gluten	½
8. E. J.	50	F	25	No	Macrocytic	110 (Fig. 2)	Yes, gluten	3½
9. A. T.	52	M	4	Small stature; rickets in childhood	Macrocytic	No change after 32 days. Normal 3 years later	No	3
10. A. B.	58	M	27	No	Macrocytic	*c.* 200 (Fig. 4)	No	1½
Clinical recovery:								
11. D. D.	33	F	9	No	Hypochromic	Not re-examined (Fig. 7*a*)	No	3
12. B. L.	36	M	2	No	Macrocytic	Not re-examined when well	No	3
13. W. J.	45	M	2	Small stature	Hypochromic	Not re-examined	Yes, wheat flour	3
14. M. P.	58	F	20	Small stature	Macrocytic	Not re-examined (Fig. 7*b*)	No	2
15. B. R.	59	F	10	No, but small stature	Macrocytic	From 40% to 85% in 150 days	Yes, inadvertently with 'arrowroot' biscuit	½ See Addendum
16. A. R. T.	68	F	6	No	Hypochromic	Not re-examined when well	No	4½

combat the diarrhoea. Potassium and sodium salts (given orally, subcutaneously, and intravenously) were used in some cases. In two patients (Nos. 10 and 15; and see Fig. 4) folic acid, cyanocobalamin (vitamin B_{12}), and corticotrophin were given with a view to speeding up the slow rate of recovery seen with the gluten-free diet alone. Of these substances only corticotrophin has been shown to have an effect in improving fat-absorption—one of the main criteria in assessing recovery—and none of the measures adopted in this manner has previously been shown to cure the condition.

Procedure. The patients were given an ordinary wheat-containing diet, with a fixed intake, for an initial control period, during which investigations were carried out to establish or confirm the diagnosis. After this the patient was given the wheat-gluten-free diet, the fat intake remaining fixed. In some cases observed for long periods the findings on the patients' previous admissions to hospital were used as evidence of the disease, and the wheat-gluten-free diet was started on admission. Besides clinical assessment, progress was estimated by daily chemical estimation of the faecal fat, regular weighings, and frequent examination of the blood picture. If recovery became evident, further radiographs of the small intestine were taken. In five cases observations were made

Explanatory note to figures.

Figs. 1 to 9 show the influence of the wheat-free diet on fat-absorption, body-weight, and fat-excretion. The absorption and excretion values shown, although plotted daily, are three-day sliding means. These eliminate major fluctuations due to irregular evacuation of the colon, or minor differences in times of collection.

Fat-intake was controlled, except at home, when fat was allowed *ad libitum*. In most cases an intake of 50 gm. was used, occasionally 70 gm. Intakes higher than this are marked on the charts.

The figures show a representative selection of patients in whom the diet has been successful (Cases 1 to 7) and failed (Cases 8 to 10), and patients in whom relapses have been induced with wheat flour or wheat gluten (Cases 1, 2, 3, 5, and 6).

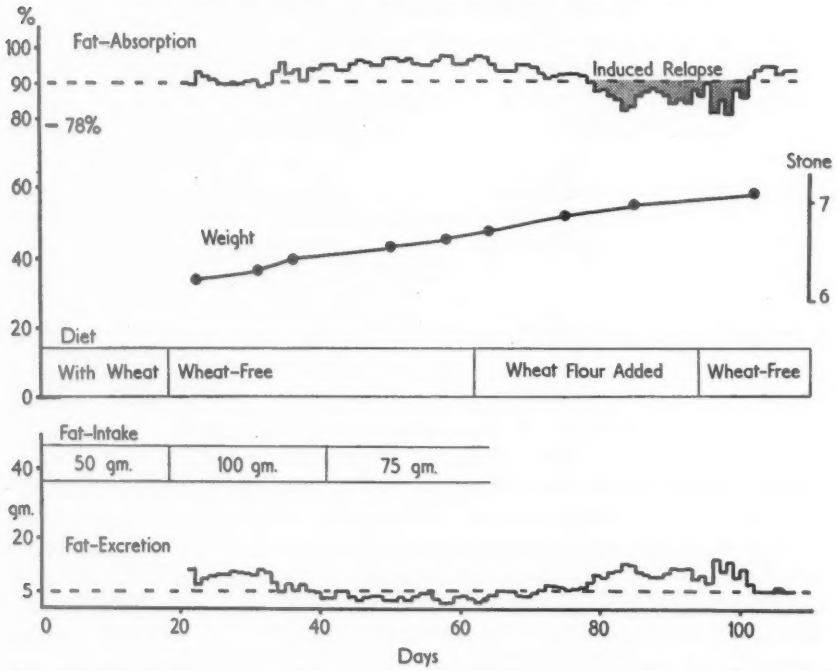

FIG. 1. Case 1. A woman aged 21, with infantilism. Improvement with wheat-free diet, with increase of weight. Relapse induced with wheat flour. Absorption returned to normal again when wheat flour was withdrawn. The patient remained well; normal sexual development occurred during the ensuing five months. Coeliac patient, but infantilism the only sign.

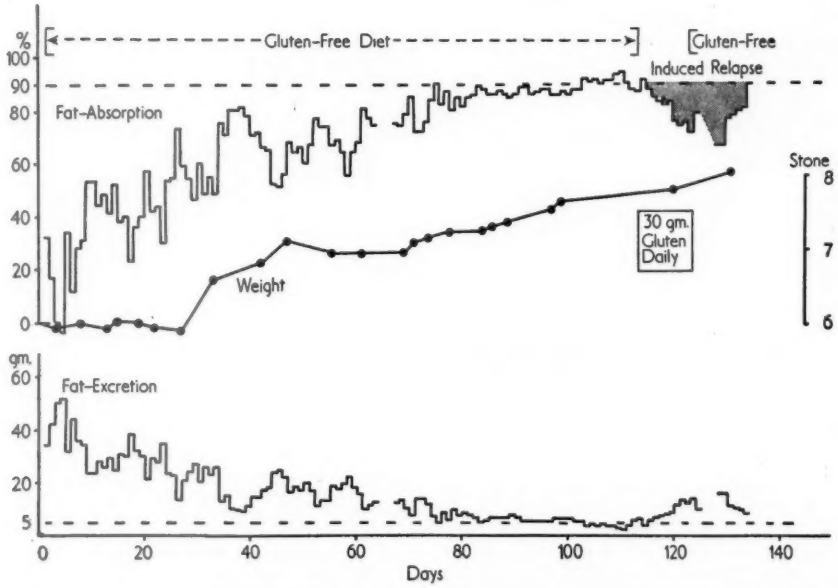

FIG. 2. Case 8. A woman aged 50; 25 years' history. Gradual improvement in 110 days to normal with wheat-free diet. Relapse induced with wheat gluten, 30 gm. daily. No symptoms since for three and a half years. No coeliac history. For blood changes see Fig. 10.

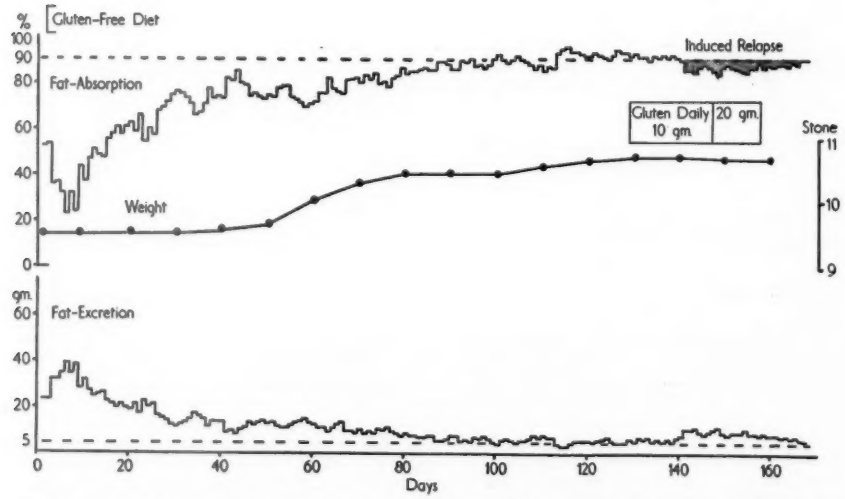

FIG. 3. Case 7. A man aged 40; 15 years' history. Diagnosed and treated originally as tropical sprue; not cured. Wheat-gluten-free diet instituted; gradual improvement to normal in 112 days. Relapse induced with bread and gluten. No coeliac history.

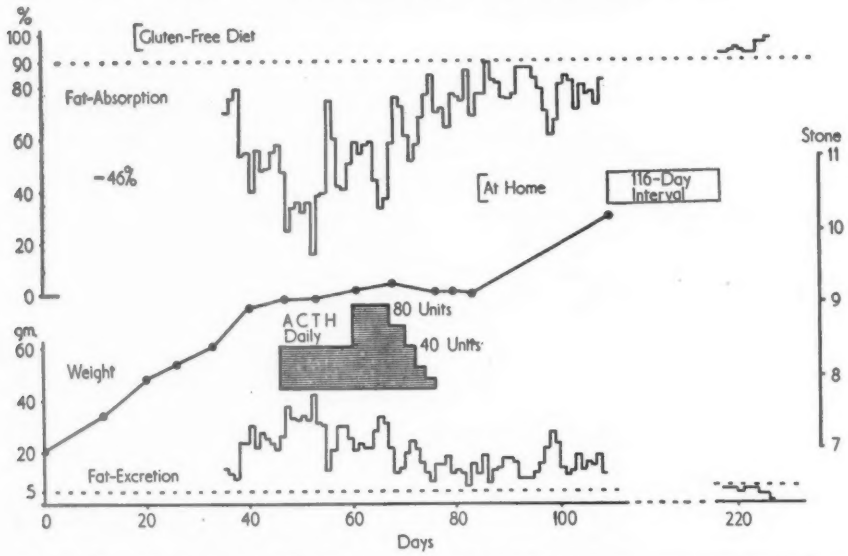

FIG. 4. Case 10. A man aged 58; 27 years' history. Gradual improvement with wheat-free diet, until absorption ultimately became normal about 200 days from the time of starting the diet.

Corticotrophin given for 30 days had no apparent effect on the course of the illness. Fat-absorption for the period at home was calculated for an estimated average intake of 70 gm. No relapse after 18 months. No coeliac history.

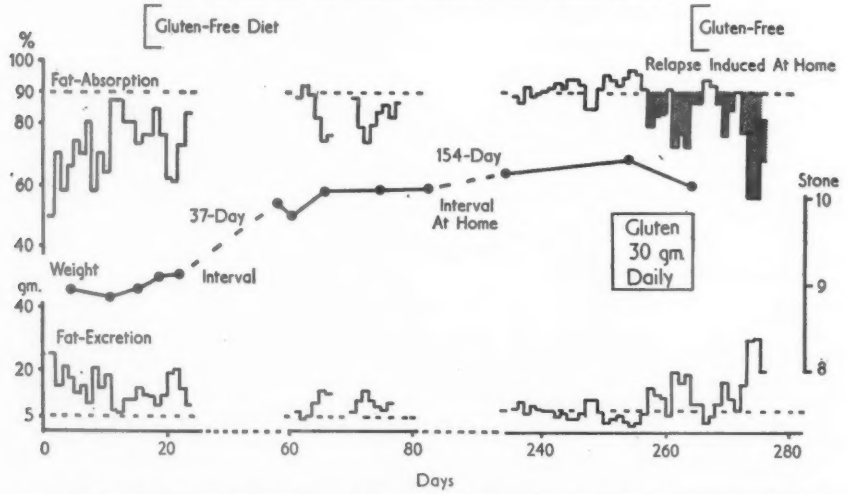

FIG. 5. Case 2. A woman aged 29; eight years' history. Gradual improvement with wheat-free diet, until absorption ultimately became normal about 200 days from the time of starting the diet. Gluten 30 gm. was then given. Loss of appetite was noticed in three days; violent diarrhoea with liquid gassy stools on the eighth day, the first liquid motion for over six months. The patient returned to gluten-free diet forthwith, and has been free from symptoms since (two years). The relapse induced with wheat gluten was associated with return of steatorrhoea and sore tongue. Fat-absorption for the period at home is calculated for an average intake of 70 gm. fat. No coeliac history.

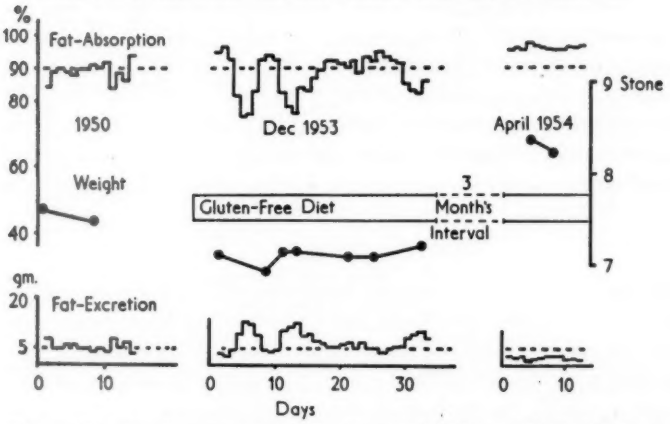

FIG. 6. Case 5. A woman aged 39; 21 years' history. Studied first in 1950. *Note slight fat-absorption defect.* Wheat-free diet instituted in 1953; little or no change in fat-absorption up to 35 days, but it was normal three months later, and the weight had increased. No coeliac history, but small stature. Remarkable changes took place in the blood picture (see Fig. 11). No relapse in three and a half years.

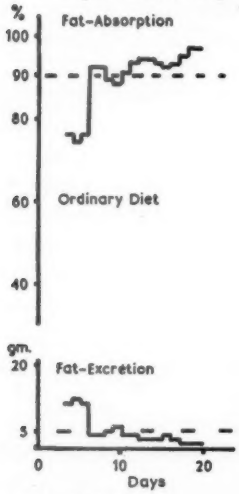

FIG. 7*a*.

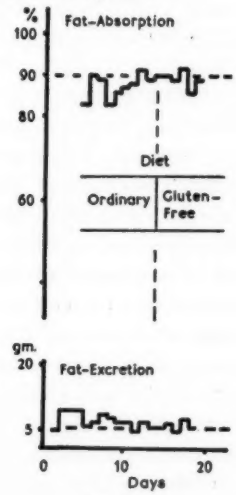

FIG. 7*b*.

FIG. 7*a*. Case 11. A woman aged 33; nine years' history. *The fat-absorption defect was found to be mild, and rapidly became normal in hospital on a diet containing 50 gm. fat and ordinary amounts of wheat flour.* Other symptoms and signs of the disease persisted, and her diarrhoea returned when she went home. Wheat-free diet instituted; remarkable changes in well being and loss of symptoms; the patient became pregnant. After delivery she was a stone above her previous weight. Improvement has been maintained, she is free from symptoms, and her blood is normal three years after recovery. No coeliac history.

FIG. 7*b*. Case 14. A woman aged 58; 20 years' history. Diarrhoea, glossitis, and skin rashes, with anaemia. *Note slight fat-absorption defect.* Three months after starting the diet she became constipated and needed laxatives. She also noticed that wheat flour, taken inadvertently, had a laxative effect lasting several days. All other symptoms disappeared, and there was a great increase in energy. Weight increased by one stone. No relapse in two years. No coeliac history.

during the reintroduction of wheat flour or wheat gluten into the diet, followed by a further period of withdrawal.

The criteria of recovery were:

(1) Disappearance of clinical symptoms, that is, loss of diarrhoea, glossitis, and stomatitis, and return of appetite and energy. (2) Gain in weight. (3) Return of the blood picture to normal. (4) Return of fat-absorption to normal.

Results

Nine patients made a complete recovery without any form of treatment other than the gluten-free diet, and the blood picture and fat-absorption (Figs. 1, 2, 3, 5, 6) both returned to normal (Cases 1 to 9). One patient (Case 10, Fig. 4), who received folic acid, cyanocobalamin, and a course of corticotrophin, also made a complete recovery. In this patient recovery, as indicated by the improvement in fat-absorption and gain of weight, appeared to take place gradually, without relation to the administration of corticotrophin or the haematinic drugs. Six further patients (Cases 11 to 16), one of whom (Case 15) also had folic acid, vitamin B_{12}, and corticotrophin, made a complete clinical and haematological recovery, but fat-absorption was not finally reassessed. All these 16 patients have since been in normal health, and the blood findings have remained normal. Their weight has remained stationary or increased since discharge from hospital. Many of them declare that they are in a better state of health than they can remember enjoying at any time, or at least for many years. The time taken to achieve normality of fat-absorption (Table I) varied in different cases, from about 20 days to about 200 days. The time during which the patients have been entirely free from symptoms since recovery is also shown in Table I. The longest period so far is four and a half years. X-rays of the small intestine showed improvement in the patients who recovered. Though some degree of flocculation was present in most cases at the time of discharge from hospital, dilatation of the intestine had disappeared. Radiographs taken at a later date in several patients have shown a further improvement, and the radiographic findings will be the subject of a separate report.

Gluten-induced relapses. In three patients (Cases 2, 7, and 8) relapses were induced under controlled conditions by giving 20 to 30 gm. of powdered dried gluten with the diet daily. Relapse was indicated by increasing anorexia, return of abdominal discomfort, increased looseness and pallor of the faeces, usually with some increase in volume, and an increase in fat-excretion on a constant intake of fat. Two healthy students, with a normal fat-excretion on an ordinary diet, who were given 30 gm. of gluten powder daily for 10 days in addition to their normal daily intake of wheat flour, showed no intestinal upset or increase in faecal fat. In two other patients (Cases 1 and 4) relapse was induced by giving about 100 gm. of wheat flour daily in the diet, and in these cases also the daily fat-excretion increased. The relapses were short-lived, and rapid improvement again took place when wheat gluten and wheat flour were excluded from the diet once more. The induced defects of fat-absorption in four cases are shown in

Figs. 1, 2, 3, and 5. These results indicate the specific effect of wheat gluten, as demonstrated also in coeliac disease. Relapses in two other cases are of interest. After treatment with the diet for two years, one patient (Case 13) was advised to try wheat flour at home. Within three weeks symptoms returned; he stopped taking wheat flour, and after a short interval became free from symptoms once more. Another patient (Case 15) was advised that she could take arrowroot. Without

TABLE II

Adult Idiopathic Steatorrhoea: Failures after a Reasonable Period of Treatment with Gluten-free Diet

Patient	*Age (years)*	*Sex*	*Duration of illness (years)*	*Any evidence of coeliac disease*	*Type of anaemia*	*Length of trial of wheat-free diet (days)*	*Remarks*
17. E. G.	46	M	16	No	Macrocytic	59	No improvement; returned to ordinary diet. Died a year later of 'inanition'
18. E. S.	50	F	45	Yes	Hypochromic	132 (Fig. 8)	Improved; subsequently relapsed while on diet, and died of pneumonia
19. D. R.	50	F	20	Much diarrhoea in childhood	Macrocytic	(i) 31 (Fig. 9) (ii) 55	No improvement; deteriorated steadily, returned to ordinary diet, and subsequently died from peritonitis (tubal abscess) while receiving cortisone
20. K. J.	50	F	10	No	Macrocytic	58	No improvement; returned to ordinary diet; chronically ill
21. W. B.	57	M	4	No	Macrocytic	(i) 117 (ii) 61	Improved both times; returned to ordinary diet, relapsed, and later died of pneumonia
22. E. W.	59	M	10	No	Macrocytic	49	Improved; fat-absorption rose from 70% to 90%; returned to ordinary diet; relapsed; chronically ill

the knowledge of the diet kitchen staff or the authors, she obtained 'arrowroot' biscuits from an outside source, and ate them in hospital. For some time it had been noticed that her symptoms were worse, and towards the end of her stay in hospital the faeces increased rapidly in volume and in fat-content. One month after discharge she declared that she was as bad as she had been on admission. She had gained a further few pounds in weight, but was daily passing large voluminous stools, and also had to get up at night for this purpose. She stated that she had been supplementing her gluten-free diet with many 'arrowroot' biscuits, as she found these a palatable substitute for the special bread. 'Arrowroot' biscuits in this country, as we have since found, are manufactured mainly from wheat flour. The patient ceased to take these biscuits, her symptoms subsided within a week, and she made a rapid gain in weight from that time. She has remained free from symptoms since. No relapses other than those described above have occurred in the patients who recovered.

Failures. Six patients failed to respond favourably to the gluten-free diet. Nothing else was observed in these cases to differentiate them from the others. Relevant details of each case are shown in Table II.

Discussion

The natural history of idiopathic steatorrhoea has always made it difficult to assess the effect of various remedies and diets, especially in short trials. There

is a constant background of malnutrition, and the clinical condition of the patients undergoes variations without apparent cause; for long periods they may be able to live normally, whereas at other times they are prostrate for weeks or months with incapacitating diarrhoea, severe anaemia, and vitamin deficiencies. Careful medical supervision, with early correction of incipient anaemia and the use of a high-protein, low-fat diet, has enabled about 70 per

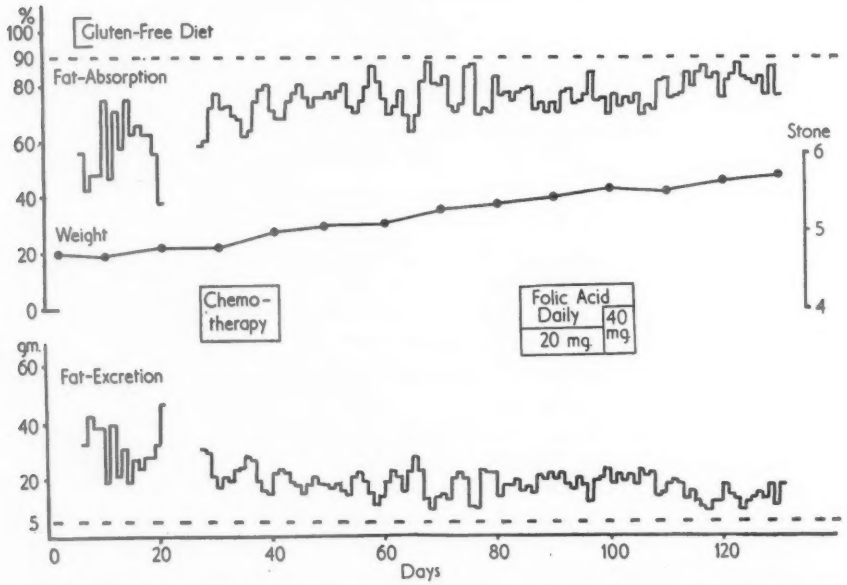

FIG. 8. Case 18. A woman aged 54; 45 years' history. Gradual increase in weight, and improvement in fat-absorption and symptoms, in 132 days. The patient returned home to continue the diet; relapsed after a year. Admitted to hospital in malnourished state; no change after a further period on wheat-free diet; she developed bronchopneumonia and died. Old coeliac patient.

cent. of patients with this disease to carry out their ordinary work satisfactorily (Cooke, 1952). Yet, however well they appear clinically, objective assessment has invariably shown a persistence of the fat-absorption defect, and frequently a macrocytosis or slight macrocytic anaemia. From observations over many years we had concluded that the abnormality of the small intestine in idiopathic steatorrhoea was a permanent, irreversible state, in which actual cure was impossible—an interesting contrast to tropical sprue, in which cure can almost always be achieved. Nor have any accounts been published of persistent disappearance of the fat-absorption defect with any type of therapy or regimen. The most successful approach has been by adrenal cortical therapy, with which there may be an improvement in fat-absorption, sometimes almost to normal levels (Taylor, Wollaeger, Comfort, and Power, 1952; Cooke, 1953), but this improvement is not maintained when the treatment is discontinued. It seems, therefore, that the complete clinical and biochemical remissions induced in 16 of

our 22 patients were due to the exclusion of gluten from their diets, rather than to any natural variations in the disease, a conclusion that is supported by the induction of relapses in five patients when gluten was given to them under controlled conditions. It also follows that the illness in these cases is analogous to coeliac disease in children, as far as aetiology is concerned, since the same sequence of events has now been shown to occur in both. The only difference in

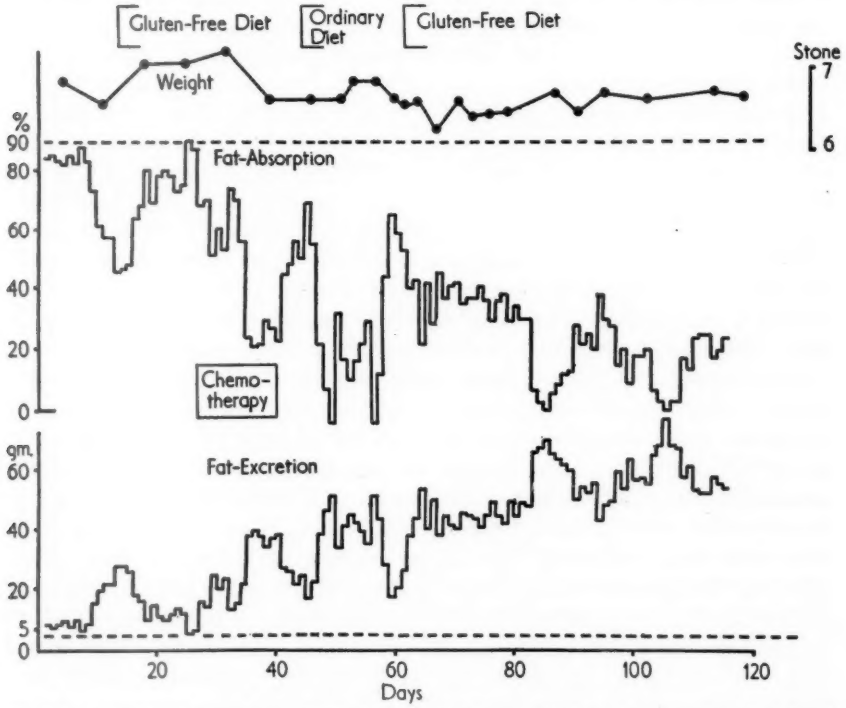

FIG. 9. Case 19. A woman aged 50; 26 years' history. Gradual deterioration thoughout the wheat-free periods, although the onset of deterioration appeared suddenly, from the time of oral administration of streptomycin: fulminating diarrhoea with a volume of three litres daily; the stools yielded a pure coccal growth. After two periods of wheat-free diet (31 and 55 days) the patient returned home on ordinary diet. Subsequently treated with cortisone; she developed peritonitis from tubal abscess, and died. Possibly coeliac patient (diarrhoea in childhood).

response that we can discern is that in children the period of recovery on a gluten-free diet is usually three to six weeks, while in adults it is often three to six months. The chronicity of the condition in most of the adult patients may explain this difference. In spite of the identity of the disease in children and adults disclosed by the present study, there are still minor differences in individual adult cases which remain unexplained on any obvious basis: in particular, the high incidence of macrocytosis in the blood in adult patients compared with children, in whom the anaemia is hypochromic and often microcytic, and the frequency of glossitis and stomatitis in the adult and their rarity in the

child. Other slight differences are probably explicable on the basis of age or length of history. From the figures given in Tables I and II it can be seen that the number of patients in whom a presumptive diagnosis of coeliac disease could be made was only nine out of the 16 who recovered and two of the six who did not. There are no obvious grounds, therefore, for believing that improvement in the adult is limited to those who have had the illness in childhood. Coeliac disease, however, in its less manifest forms may be difficult to detect, and it is still possible that in the remaining patients signs had occurred in childhood which were never observed because they were insufficient to give rise to symptoms.

'*Tropical sprue.*' Two patients (Nos. 17 and 7) included in this series had been ill for 16 and 15 years respectively. Both had been treated for as many years with the various remedies in vogue for sprue, as their illness had begun in the tropics. This treatment included high-protein, low-fat diet, B vitamins, including nicotinic acid, riboflavin, and cyanocobalamin, folic acid, and liver extract, without effecting a cure. Patient No. 17 showed no improvement on the gluten-free diet, and refused further treatment after 59 days. Patient No. 7, however, showed a complete recovery, followed by a relapse with administration of gluten, and recovery again on its cessation (Fig. 3). It is evident that he was a gluten-sensitive subject. Tropical sprue, because of its liability to occur in epidemic form (Ayrey, 1947), does not appear to be associated with gluten sensitivity, and there is general agreement that patients with sprue get completely well with treatment in a temperate climate when wheat flour is a normal constituent of the diet. In three cases of tropical sprue (unpublished) we have observed that when gluten was withheld for one month no improvement took place until other treatments were given; and a more significant observation was that, when gastrointestinal function had been restored to normal, readmission of wheat flour to the diet did not result in any deterioration during a period of more than one month. Although this evidence was derived from only three cases, similar observations have been made by others in cases of tropical sprue (Webb, 1956). It thus seems fairly certain that tropical sprue is not associated with wheat sensitivity. Although one of our 'sprue' patients (No. 17) failed to respond to the gluten-free diet, from the results in Case 7 the inference is clear: patients with tropical sprue who fail to improve after treatment for a short period in a temperate climate must be regarded as potential sufferers from idiopathic steatorrhoea, who have happened to be in the tropics at the time of the onset of the illness.

Slight defects of fat-absorption. The response of four other patients (Nos. 1, 5, 11, and 14) merits special discussion. The diagnosis of idiopathic steatorrhoea in most cases presents no difficulty, provided that the fat balance clearly shows a fat-absorption defect to be present. Sometimes, however, fat-absorption is nearly normal, as in these four cases. Three-day balances showed that it was sometimes below and sometimes above 90 per cent. at the time of investigation (Figs. 1, 6, 7*a*, 7*b*), though symptoms had persisted for many years. This slight defect was quite out of keeping with the other facets of the disease, such as loss

of weight, lack of energy, sore tongue, anaemia, and, in Case 1, infantilism as well. Any doubt that the patients belonged to this group was dispelled by the striking results obtained after the institution of the gluten-free diet. There was a great change in sense of well-being and an increase in weight; the bowels became costive, the frequent episodes of glossitis disappeared, the blood picture became normal, the patients' appetite improved greatly, and they could eat as much fat as they liked without return of any of their symptoms. As regards sexual function, in one case frigidity, which had been a troublesome feature of married life for many years, disappeared, another patient became pregnant for the first time after eight years of married life (a similar change was observed in Case 6), and another patient (Case 1) underwent complete puberal changes, with normal development, in about five months. These events strongly suggest that steroid chemistry in these patients, which had been faulty before, had returned to normal with the restoration of normal gastrointestinal function. Apart from the phasic nature of the illness, which is not easily explicable, the most likely explanation of the slightness of the absorption defect, in association with other fairly pronounced symptoms and signs of the condition, must be that a fat-absorption defect becomes demonstrable with present methods only when there is considerable disablement of small-intestinal function. As in most other organs, there must be a functional reserve which prevents accurate estimation of absorptive capacity simply by the estimation of faecal fat in relation to dietary intake. Two things emerge clearly from the study of these four patients. First, if the diagnosis of idiopathic steatorrhoea is to stand or fall by the demonstration of an excess of faecal fat, a three-day balance period may be inadequate in some cases; X-ray films of the small intestine, which showed flocculation in all the above cases, are a valuable deciding factor in the diagnosis. Secondly, the diet should be given a trial even in patients in whom a fat-absorption defect appears to be negligible, if other factors point to a diagnosis of idiopathic steatorrhoea.

The anaemia. Haematopoietic substances, such as folic acid, folinic acid, and vitamin B_{12}, are commonly used to treat the anaemia of idiopathic steatorrhoea. Folic acid, however, is poorly absorbed in such cases when given by mouth (Girdwood, 1953), and completeness of absorption must depend, at least to some extent, on the absorptive capacity of the small intestine. This capacity is known to be impaired in varying degrees in cases of idiopathic steatorrhoea in which fat-absorption has been shown to be defective. From an examination of the widely differing absorptive states (as shown by fat-absorption) in various patients, and of the variations in different periods in the same patient, it is apparent that any studies of the effect of oral haematopoietic substances, such as folic acid, must take such variations into account if they are to be significant. Consequently much past work with these substances given orally would seem to be of doubtful value. In treating our patients the impairment of absorptive capacity was taken into account, and doses of folic acid were given far in excess of normal requirements.

The anaemia of idiopathic steatorrhoea, although frequently macrocytic

owing to deficiency of folic acid or vitamin B_{12}, or both, often shows signs of iron deficiency also. Correction of the iron deficiency makes the macrocytosis more pronounced (Hawkins, Peeney, and Cooke, 1950). Treatment of the anaemia with vitamin B_{12} and folic acid, with or without ascorbic acid, usually results in some improvement, especially when the anaemia is severe and the bone-marrow shows megaloblasts, but it is unusual for the blood picture to

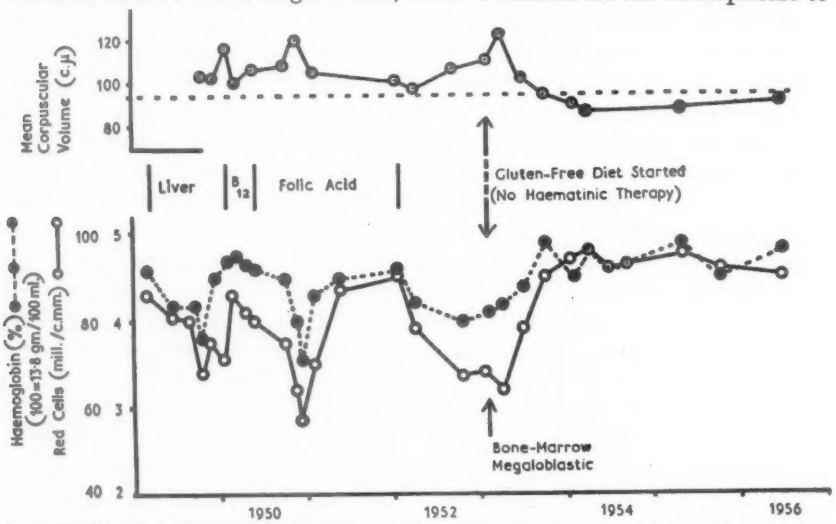

FIG. 10. Blood changes with wheat-free diet (Case 8). A woman, aged 50 in 1953, who had been treated for 'pernicious anaemia' since 1945. In spite of liver injections, cyanocobalamin, and folic acid, a macrocytic anaemia persisted. It disappeared on a gluten-free diet, and the blood has remained normocytic for over four years. See also Fig. 2 for details of fat-absorption.

become completely normal, and if it does so it fails to remain normal if administration of haematopoietic substances is not continued. Commonly, in spite of continued administration, the haemoglobin remains at about 80 per cent., and macrocytosis persists, as in Cases 8 and 5 (Figs. 10 and 11). It is probable, from the few results we are able to show in this series, that the institution of the gluten-free diet leads to permanent improvements in the blood picture exceeding those which may be obtained with folic acid, vitamin B_{12} or liver extracts; and improvements may occur quite rapidly (Figs. 10 and 11). This change could conceivably be related to better absorption, although in these two patients striking improvement quickly took place before absorption became completely normal. If an ordinary diet, with injections of vitamin B_{12}, or oral treatment with folic acid in doses large enough to ensure the absorption of adequate amounts, failed to restore the blood picture to normal, and, on the other hand, a gluten-free diet without added haematopoietic substances resulted in normal blood regeneration, it would seem that malabsorption of the known haematopoietic factors is not entirely responsible for the macrocytic anaemia. Some toxic arrest of blood maturation seems likely (Ungley, 1951–2), perhaps from intestinal putrefaction.

Mechanism of defective absorption. Dicke, Weijers, and van de Kamer (1953) showed that administration of wheat protein (whole gluten or the gliadin fraction) to coeliac children, who had recovered on a wheat-free diet, caused rapid deterioration of the general clinical state, with loss of weight, onset of diarrhoea, and an increase in faecal fat, leading to a condition which was indistinguishable from the original illness; and their results have been fully confirmed in this

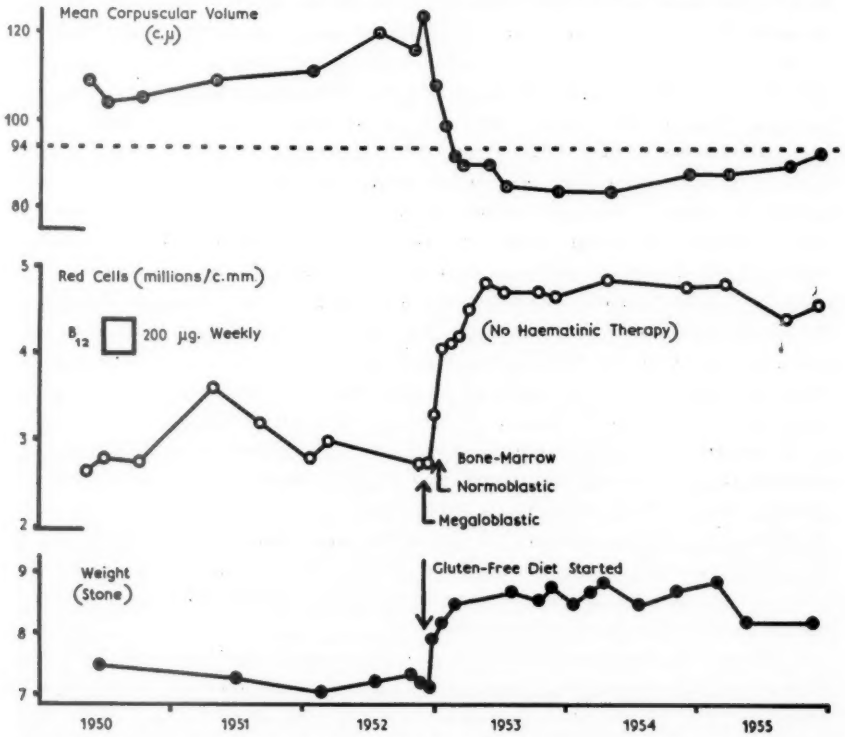

FIG. 11. Blood changes with wheat-free diet (Case 5). A woman aged 38, with macrocytic anaemia resistant to vitamin B_{12} given for three months. The gluten-free diet was started during a relapse in the anaemia, when the bone-marrow was megaloblastic; it showed normal erythropoiesis within one month. Note the rapid rise in red-cell count and haemoglobin, with loss of macrocytosis. The blood has remained normal during three years without treatment except gluten-free diet. See also Fig. 6 for details of fat-absorption.

country. It seems difficult to believe that a protein so universally consumed in large quantities could be toxic to a few individuals, except on an allergic basis, though there is little evidence to support such a theory. Allergic phenomena such as asthma, eczema, hay fever, or urticaria do not seem to be a feature of coeliac disease, though eczematous rashes are seen fairly frequently in idiopathic steatorrhoea. Wheat and rye flour, which both cause deterioration in coeliac disease, also both make dough suitable for bread-making: maize and rice, although containing gluten, can be given in any quantity to coeliac children without causing deterioration, but do not make dough. The dough-making

properties depend ultimately upon the chemical constitution of the gluten. This association, therefore, seems to point to some peculiarity in chemical structure which is responsible for the effect in coeliac disease. This possibility is further emphasized by an antigenic relationship which has been demonstrated between wheat and rye gluten (and also barley) by the induction of allergic and immunological phenomena in guinea-pigs; more significantly, this cross-relationship does not extend to maize gluten (Wells and Osborne, 1911; Lake, Osborne, and Wells, 1914). An alternative explanation is that some constitutional abnormality of the coeliac child, such as the failure to digest a specific protein, may lead to the development of toxic substances, perhaps by intestinal bacteria, though there is no evidence as yet to suggest that this occurs.

It seems possible that soluble breakdown products of wheat and rye gluten cause a tissue reaction of an allergic nature in the small intestine, resulting in an increased secretion of mucus which delays absorption, but does not interfere with digestion. Removal of the offending allergen from the diet leads to recovery of the mucous membrane, and also the rate of absorption, to a normal state. Delayed absorption is characteristic of the condition, however, whatever the initial mechanism, and delay in the absorption of food may have two possible sequelae: first, nutritional deficiencies may develop, and there is abundant evidence that they do in most cases; and secondly, an increased growth of bacteria may occur in the lumen. Evidence of the latter effect is indirect, such as the presence of increased products of bacterial fermentation in the stools, although it has also long been recognized that the faecal bacteria are abnormal (Herter, 1908). If the relatively simple allergic situation suggested above were complicated by either or both of these effects, mere removal of gluten from the diet might not lead to a reversal of the changes in the small intestine and recovery of the patient. There are therefore several possible explanations for the lack of recovery in six of our patients.

1. The period of trial may not have been long enough. It may be seen from the other cases that the recovery period may be as long as 200 days, though some indication of a favourable response was usually seen within about six weeks. Although all six patients were taking a gluten-free diet for less than 200 days, the period was two months or more in each case, and only patient No. 22 showed substantial improvement in fat-absorption during that time. The possibility must also be considered that the diet was not entirely free from gluten in these cases. In some instances the full co-operation of the patient was not at all times obtained, and extra food in the form of sandwiches or biscuits was surreptitiously supplied by relatives or friends, a fact which was only found out accidentally. As coeliac disease may relapse with as little as 1 gm. of gluten daily, such action might hold up recovery indefinitely; several patients, who were to have been included in the present study, had to be excluded because they refused to co-operate in adhering strictly to the diet, although it could not be considered unpalatable. As far as we could ascertain, however, no extra diet was being taken in the cases shown as failures.

2. These patients may have been sensitive to substances in the diet other

than wheat and rye gluten. So far, no other cereal has been thought to cause the manifestations of coeliac disease, although the Dutch workers regarded oats as suspect (Dicke, Weijers, and van de Kamer, 1953). They also withheld beans from coeliac children, as the husks caused increased diarrhoea (Weijers, 1956). No factual data have been published incriminating any other substance in coeliac disease, and almost every case responds to the withdrawal of only wheat and rye from the diet.

3. Deficiency of vitamins or other essential factors may have prevented recovery. Full vitamin supplements were given to all the patients in whom failure was apparent, without causing improvement. Of the patients who recovered, Nos. 10 and 15 had full vitamin supplements, including folic acid and vitamin B_{12}, but their rates of recovery were just as slow (Fig. 4) as those seen in many patients without such supplements. Correction of the disturbed electrolyte balance assisted several patients over a critical period, but did not otherwise seem to influence the subsequent slow rate of recovery.

4. Infection of the gastrointestinal tract, especially the small gut, with pathogenic organisms, or an increase in growth of organisms regarded as normal inhabitants, as a sequel to the increased content of unabsorbed food, must be considered. It seems very likely that acute diarrhoea, due to infection of the small intestine with food-poisoning organisms or staphylococci, causes defective absorption. Data are lacking on this subject, mainly, no doubt, because of the difficulties inherent in the study of acute infections in which the main line of treatment is to withhold all food. Pathogens, however, have been so seldom grown by culture from the duodenum or faeces in idiopathic steatorrhoea, that their presence must be regarded as a coincidence. Whether an increased growth of normal intestinal organisms would interfere with absorption, and whether such increased growth is in fact present, is a matter for further investigation; no satisfactory data of a direct nature are available. There is, however, increasing evidence, in closely related types of steatorrhoea, that alterations of gastrointestinal flora resulting from the use of antibiotics lead to changes in the absorptive capacity of the small intestine. In tropical sprue suppression of the intestinal flora with a course of several antibiotics has led to a return of fat-absorption to normal and to cure of the illness (French, Gaddie, and Smith, 1956); somewhat similar observations have been made in the steatorrhoea associated with diverticulosis of the small intestine (Dick, 1955; Blachford and Dawson, 1956), and in other steatorrhoeas of a sprue-like nature (Renner, 1952; Caroli, 1956). On the other hand, it has been claimed that orally administered antibiotics actually cause steatorrhoea (Merliss and Hoffman, 1951). If intestinal flora are in any way connected with defective absorption, the explanation of failure may lie here.

5. Some disease other than idiopathic steatorrhoea may have been responsible for the failure of absorption. Two of the four patients who died were examined *post mortem*, and the pathological appearances were non-specific, as in idiopathic steatorrhoea. It is possible that in the other cases steatorrhoea was secondary, as in malignant disease of the small intestine or Whipple's disease. Two patients,

not included in the present series, were treated for some months with a gluten-free diet without improvement, and subsequently died. Post-mortem examination showed reticulosarcomatous infiltration of the small intestine. Laparotomy in patients who fail to respond to a gluten-free diet seems justified to exclude other diseases. Lastly, it is possible that these patients comprise a group with non-specific jejuno-ileitis, a recently recognized disorder in which diagnosis depends on the exclusion of cases which respond to a gluten-free diet. Further study is needed to elucidate these various factors.

We wish to express our thanks to Professor W. Melville Arnott for his advice, help, and encouragement, and to the Physicians of the United Birmingham Hospitals, without whose valuable assistance and co-operation this study could not have been undertaken; to Sisters S. Churton, D. Bayliss, L. Gordon, and other members of the Nursing Staff of the Queen Elizabeth and General Hospitals; to the dieticians, especially Sisters E. Richards and P. M. Leach, and Miss A. McLellan; to Dr. R. Gaddie and Mr. Garfield Thomas, for assistance with the biochemical investigations; and to Dr. M. J. Meynell, Dr. J. N. M. Chalmers, and the late Dr. A. L. P. Peeney for the haematological investigation.

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Summary

Twenty-two patients with idiopathic steatorrhoea were treated with a wheat-gluten-free diet. Sixteen recovered completely. Ten of these 16 patients were investigated later, and the fat-absorption and blood picture were found to be normal. (See Addendum.)

Five of the patients who recovered were given gluten or gluten-containing food for a short period while under dietary control. Within a few days appetite decreased, the stools became looser and paler, symptoms returned, and fat-excretion again became abnormal, indicating a relapse. Withdrawal of the gluten resulted in a return to normal health.

Six patients failed to recover with a gluten-free diet; although improvement was seen in some of these patients, five elected to return to an ordinary diet. Four of them have since died from complications of the illness. The remaining two are still in a state of ill health.

It is concluded that (1) in most cases the reaction to wheat gluten is the basic cause of idiopathic steatorrhoea, as most but not all patients respond favourably to a gluten-free diet; (2) a favourable response in adults is slower than in children, and the diet cannot be regarded as having failed unless a trial period of at least six months has been given; (3) once normal health has been regained, the gluten-free diet must be continued indefinitely in order to avoid relapse.

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ADDENDUM

Patient No. 15 (Table I) has since relapsed, one year after apparent recovery.

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TOTAL ADRENALECTOMY FOR SEVERE HYPERTENSION[1]

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With Plate 45

MANY facts and hypotheses relate the functional activities of the adrenal cortex to the level of the blood-pressure. Goldblatt (1937) and Blalock and Levy (1937) observed that ischaemic renal hypertension was abolished in dogs by adrenalectomy, and that this effect was due to removal of the adrenal cortex rather than medulla. It was later confirmed that treatment of these animals with salt and cortical extract led to a return of the hypertension (Page, 1938; dell' Orro, 1942). Verney and Vogt (1938) demonstrated that renal hypertension in dogs with intact adrenal glands was aggravated by increasing the dietary intake of sodium. Conversely sodium restriction was found to lower the blood-pressure of rats with renal hypertension (Grollman and Harrison, 1945). The synthetic adrenocortical steroid, deoxycorticosterone, has been shown to have a pressor effect in both normal dogs (Kuhlmann, Ragan, Ferrebee, Atchley, and Loeb, 1939) and rats (Grollman, Harrison, and Williams, 1940), and will maintain renal hypertension in animals deprived of their adrenals (Page, Ogden, and Anderson, 1946; Wilson, 1953). It has been found to cause severe hypertension in nephritic rats when given in a dose which is too small to have a pressor effect in normal animals (Knowlton, Stoerk, Seegal, and Loeb, 1946) and, if given in large doses to normal animals on a high salt intake, it may cause severe nephrosclerosis and hypertension (Selye, 1942; Selye, Hall, and Rowley, 1943; Selye and Hall, 1944). The implication of the adrenal cortex in experimental renal hypertension obtains further corroboration from the observation that the hypertension is abolished by hypophysectomy in dogs (Page and Sweet, 1936) and rats (Leathem and Drill, 1944), and that administration of adrenocorticotrophic hormone to these animals is associated with a return of hypertension (Anderson, Page, Li, and Ogden, 1944). Corollaries to these experimental observations are found, in the human subject, in the hypotension of Addison's disease and in the frequency with which hypertension is encountered in adrenocortical overactivity. It has been observed that patients with essential hypertension who subsequently develop Addison's disease may show a substantial fall in blood-pressure (Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt, 1952; Perera, 1945) and, conversely, that excessive administration of deoxycorticosterone or cortisone to

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patients with adrenocortical insufficiency may sometimes produce considerable hypertension (Loeb, Atchley, Ferrebee, and Ragan, 1939; Thorn, Dorrance, and Day, 1942; Roth, Robinson, and Wilder, 1943). The evidence that the adrenal glands play a role in the regulation of blood-pressure is so strong that it is not surprising that many attempts have been made to treat hypertension by their removal.

The first attempt at adrenal surgery in patients with hypertensive disease was made in 1914, when Crile (1936) combined unilateral adrenalectomy with various other surgical procedures. DeCourcy, DeCourcy, and Thuss (1934) described six patients in whom subtotal bilateral adrenalectomy had been performed for hypertensive disease on the assumption that the adrenal medulla might be responsible. Total bilateral adrenalectomy was impracticable, however, until cortisone became available, and since then there have been many reports of total or subtotal adrenalectomy, usually combined with various types of sympathectomy (Neuhof, 1948; Wolferth, Jeffers, Lukens, Zintel, and Hafkenschiel, 1951; Jeffers, Zintel, Hills, Hafkenschiel, Langfeld, Sellers, and Wolferth, 1954). Unfortunately these combined operations allow of no critical evaluation of the part that adrenalectomy plays in the results.

Green, Nelson, Dodds, and Smalley (1950) were the first to describe the resolution of malignant hypertension after total adrenalectomy, in a woman with diabetes mellitus. In 1952 Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt described the effects of total adrenalectomy alone in the treatment of hypertension, in the only large series reported so far. Ten patients with malignant or severe essential hypertension, and five with chronic glomerulonephritis, were subjected to operation. Six died in the period immediately following operation or in the succeeding four weeks, and of the nine patients surviving for longer only four showed some fall in blood-pressure, in no case to normal levels. Another three, who showed no fall in blood-pressure, were said to be improved. Four of the nine survivors died in the year following operation, three from the natural consequences of the disease and one apparently from acute adrenal insufficiency; two of these were patients in whom the blood-pressure had fallen. At the end of one year only five out of the total of 15 patients originally subjected to operation were still alive; two of these had benign and two malignant hypertension, and one had chronic glomerulonephritis. In only two of these five survivors was the blood-pressure lowered significantly. The retinitis which had been present before the operation in three of the five survivors had resolved in one, and was unchanged in one; no details are given for the third. There are insufficient data to assess the effect on the proteinuria. Of the nine patients who survived operation longer than four weeks, five showed an increase of blood-urea, which persisted in four; the level eventually returned to normal in the fifth. Bowers (1954) described the effects of partial adrenalectomy in 26 patients with essential hypertension; although all are reported to have shown a fall in blood-pressure, the data given are insufficient to assess accurately the results of the procedure.

Pickering, Wright, and Heptinstall (1952) were the first in this country to record their experience of partial adrenalectomy for hypertension. Two girls,

aged 11 and 13 years respectively, who had malignant hypertension associated with chronic pyelonephritis, were treated by subtotal adrenalectomy combined with splanchnicectomy and ganglionectomy. The elder had had one kidney removed nine months before, without effect on her blood-pressure. In both patients the papilloedema and retinitis subsided, but only in the younger child was there any substantial reduction of blood-pressure, and it was still considerably reduced six years after operation. They also described a 33-year-old man, with malignant hypertension associated with pyelonephritis, whose blood-pressure fell considerably after the right kidney and adrenal gland were removed and a right splanchnicectomy was performed. Pickering and Heptinstall (1953) subsequently described a 10-year-old boy, with pyelonephritis and malignant hypertension, in whom one adrenal gland was first removed, and later most of the other; this treatment had no effect on his blood-pressure, although his neuroretinitis disappeared soon after the second operation. These authors also stated that subtotal adrenalectomy had been employed unsuccessfully for the treatment of three adults with malignant essential hypertension. Two died soon after operation, and the third showed little change in blood-pressure, but no other details are given. Rosenheim (1954) described the effects of total adrenalectomy in two patients with essential hypertension, in one of whom it was of the malignant type. In the latter case the blood-pressure is said to have risen when 50 mg. of cortisone was given daily by mouth, but no figures are reported, except that after a severe gastrointestinal haemorrhage the blood-pressure was still 180/120. Illustrations of the optic fundi before and after operation, however, show a great improvement. The blood-pressure of the other patient, with severe essential hypertension, appeared to be little affected by the operation, even when adrenocortical insufficiency supervened. The treatment prescribed for neither patient is detailed. Wilson (1955) reported the effect of total bilateral adrenalectomy in a patient with carcinoma of the prostate who had benign essential hypertension. When he was given a daily oral dose of 75 mg. of cortisone the blood-pressure was maintained at the level observed before operation, but no other information is given.

Most of the reports which have been reviewed are inconclusive. In those of Allen and Adson (1937), Neuhof (1948), Wolferth, Jeffers, Lukens, Zintel, and Hafkenschiel (1951), Pickering and Heptinstall (1953), and Jeffers, Zintel, Hills, Hafkenschiel, Langfeld, Sellers, and Wolferth (1954), the combined operations employed allow of no critical assessment of the part played by adrenal resection alone. In those of Bowers (1954), Rosenheim (1954), and Wilson (1955) the data are not sufficient to assess accurately the effect of adrenalectomy on the hypertensive state. The series reported by Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt (1952) is the most comprehensive, but the lack of detailed observations after operation again does not permit a precise assessment of the value of adrenalectomy in the treatment of hypertensive disease. Nevertheless, it was considered that the experimental evidence relating the adrenal cortex to the hypertensive state was so strong, and the prognosis of malignant hypertension so poor, that it was justifiable to undertake a limited trial of total

adrenalectomy alone in patients who had failed to respond to the more conventional forms of treatment, and to this end six patients have been studied.

Methods

Selected patients were admitted to the Medical Unit, and a series of tests was carried out to furnish data of cardiovascular, renal, and adrenal function. Blood-pressure was recorded at frequent intervals, and tests were carried out to establish the diagnosis, during a period of three weeks of restricted activity. Subsequently those patients who had no evidence of nephritis or endocrine disease were subjected to intensive treatment with oral or parenteral antihypertensive drugs, and only those were selected who had failed to respond satisfactorily or were intolerant of effective therapy in the face of rapidly advancing disease. Severe renal failure was the only absolute contra-indication to adrenalectomy. Medical students recorded the blood-pressure with a sphygmomanometer every two hours, day and night, throughout the period of observation. The readings were checked daily by a member of the team, and at intervals by direct measurements with an intra-arterial needle or catheter. Electrocardiographs and standard radiographs of the chest were taken at intervals. The heart was catheterized before operation in four of the patients, to ascertain more accurately the degree of cardiac reserve. Benzodioxane tests were carried out on all patients to exclude the presence of a phaeochromocytoma.

Quantitative estimations of the urinary protein were carried out daily, and urine concentration tests at frequent intervals before and after operation. The renal clearance of endogenous creatinine was estimated in three patients. The balance of water, sodium, potassium, and nitrogen was estimated daily. Patients were allowed a free diet; the weight of each food was noted, and a weighed sample analysed for the relevant elements. Fluids also were unrestricted, and the fluid balance was calculated on the intake of water and its excretion in the urine and faeces and in any vomitus that occurred. The loss of fluid in the sweat and the insensible loss of water through the respiratory tract were not included. All urine and faeces were collected in 24-hour samples, and portions analysed daily for sodium, potassium, chloride, and nitrogen. Sodium and potassium in both instances were estimated by flame photometer. Urine nitrogen was measured as urea by the hypobromite method, and faecal nitrogen was estimated by the method of Kjeldahl. Completeness of the urine collection was checked by estimation of the total creatinine content in each 24-hour sample. Samples of venous blood were analysed daily or on alternate days for sodium, potassium, chloride, and urea, and at less frequent intervals for calcium, phosphorus, alkaline phosphatase, proteins, and lipids. 17-ketosteroids were estimated by a micro-method based on the procedure of Zygmuntowicz, Wood, Christo, and Talbot (1951), using the colour correction suggested by Talbot, Berman, and MacLachlan (1942). All patients were weighed at intervals of three to seven days on the same chair-scales.

TABLE I

Summary of Clinical Data

Case number, sex, and age (years)	*Duration of hypertensive symptoms (years)*	*Symptoms on admission*	*Grade of cardiac disability**	*Blood-pressure on admission (72 hr. record)*		*Radiological cardiac enlargement†*	*Electro-cardiogram‡*	*Optic fundi§*	*Urine*		*Body weight (kg.)*
				Mini-mum	*Maxi-mum*				*Protein (gm./24 hrs.)*	*Maximum specific gravity (12 hrs.)*	
1 F. 39	4	Headache. Dyspnoea on exertion. Orthopnoea. Blurring of vision	III B	230/130	270/160	++++	Sinus rhythm. L.V.P.	P+R	0·50–1·00	1,024	50
2 F. 41	12	Headache. Dyspnoea on exertion	III A	190/120	250/160	++	Sinus rhythm. L.V.P.	P	0·05–0·10	1,022	84
3 F. 26	7	Headache. Dyspnoea on exertion. Blurring of vision	III A	200/140	250/170	++	Sinus rhythm. L.V.P.	P	0·40–0·50	1,020	61
4 M. 37	1	Headache. Dyspnoea on exertion. Orthopnoea. Blurring of vision	III B	200/130	240/170	+++	Sinus rhythm. L.V.P.	P+R	0·50–0·75	1,021	82
5 M. 41	6 months	Headache. Dyspnoea on exertion. Orthopnoea. Blurring of vision	III B	160/120	280/200	++++	Sinus rhythm. L.V.P.	P+R	0·50–1·00	1,014	81
6 F. 37	1	Headache	III A (?)	210/130	250/170	+	Sinus rhythm. L.V.P.	P+R	0·20–0·40	1,018	44

* The clinical grading of disability used is in accordance with that of the American Heart Association, except that Grade III is subdivided into A and B. Patients with Grade III A disability are able to walk more than a mile on the flat at their own speed, and can ascend stairs without undue discomfort. Many such patients can still earn a livelihood or perform most household tasks.

† Cardiac enlargement: + slight to ++++ very severe.

‡ L.V.P. = left ventricular preponderance.

§ P = papilloedema; R = retinal haemorrhages and exudates.

Clinical Features

The main clinical features of the patients selected for operation are given in Table I. The age of the six patients, four women and two men, ranged from 26 to 41 years at the time of operation. All were suffering from severe hypertension, and had a diastolic blood-pressure of more than 120, proteinuria, and papilloedema. None had a detectable primary renal lesion. The duration of symptoms varied from less than six months to more than 12 years. Headache was invariably present, and was the major complaint in four of the six patients; in one it was the sole presenting symptom. Dyspnoea on exertion was a major complaint in all but one patient, and was the primary presenting symptom in two. Three patients had a severe reduction, and two a moderate reduction, in their capacity for exercise. It was impossible to assess accurately the capacity of one patient because of a recent hemiplegia. Three had oedema of the ankles in the evenings and orthopnoea; one also suffered from paroxysmal nocturnal dyspnoea. Blurring of vision was present in four, and nocturia in five patients. Symptoms of coronary, cerebral, or peripheral vascular disease were present in only one patient, who had had two attacks, presumably of cerebral thrombosis, in the preceding 12 months.

The heart in all patients was in regular rhythm on admission, and none had tachycardia at rest. The blood-pressure was grossly elevated in all. The maximum and minimum values of a two-hourly record taken during the first 72 hours after admission are shown in Table I; all patients showed a marked lability of both the systolic and diastolic pressures. The effects of rest in bed are summarized in Table II. In one patient the period of rest without other treatment was 20 days, and in the others it was 30 days, but in none did the pressure fall greatly during this time. The heart was enlarged in all, varying from slight left ventricular hypertrophy to gross cardiac enlargement. Three patients with gross enlargement had a severe degree of impairment of capacity for exercise. Bilateral papilloedema was present in all patients, and accompanied by retinal haemorrhages and exudates in four. The radiological and electrocardiographic findings are summarized in Table I.

The level of haemoglobin, the erythrocyte and leucocyte counts, and the erythrocyte sedimentation rate, were normal in all patients. Two had slightly increased blood-urea, but all other biochemical values in the serum of all patients were within normal limits. Five patients had erythrocytes in small numbers in the urine, and all had granular and hyaline casts. No pus-cells were seen, and the urine, subjected to culture on frequent occasions, was found to be sterile. The proteinuria varied greatly from patient to patient, with a range of 0·05 gm. to 1 gm. per day, and was roughly proportional to the changes in the optic fundi. The urine of four patients who were deprived of water for 12 hours had a maximum specific gravity of 1,020 or more; in the other two it was 1,018 and 1,014 respectively. Endogenous creatinine clearance was reduced in two of the three patients examined, but was normal in one of the two patients who were unable to concentrate their urine. The intravenous pyelogram was normal in all, but the dye excretion was moderately reduced in one patient.

The average daily intake of water was 1·5 to 3 litres, and the output in the urine and faeces was 0·75 to 2 litres per day less than this. The balance of sodium, potassium, and nitrogen before operation was normal in all patients. The average daily intake of sodium ranged from 80 to 160 mEq., and the excretion in urine and faeces was 10 to 40 mEq. less. The average daily intake of potassium

TABLE II

Blood-Pressure before Operation

Case number	*After admission*		*After 10 days*		*After 20 days*		*After 30 days*	
	Minimum	*Maximum*	*Minimum*	*Maximum*	*Minimum*	*Maximum*	*Minimum*	*Maximum*
1	230/130	270/160	230/130	270/150	230/130	270/160	230/130	270/160
2	190/120	250/160	180/120	230/150	190/120	210/130	190/120	220/150
3	200/140	250/170	180/130	230/170	170/130	220/160	..	..
4	200/130	240/170	190/120	240/160	180/130	240/170	180/130	240/170
5	160/120	280/200	200/160	240/180	200/130	250/190	190/130	250/160
6	210/130	250/170	210/140	240/160	180/120	240/160	190/130	220/160

was 50 to 80 mEq., and the excretion in the urine and faeces 10 to 30 mEq. less. In four patients in whom nitrogen balances were studied the average daily intake ranged from 4 to 16 gm., and the excretion in the urine and faeces ranged from 3 to 11 gm. per day. The daily faecal excretion of nitrogen never exceeded 1·5 gm.

The Operation

Digitalis or mercurial diuretics were not given before operation. Each patient received 50 to 150 mg. of cortisone acetate orally on the day before, and 100 mg. three hours before the operation. Anaesthesia was induced with intravenous thiopentone, and maintained with a mixture of nitrous oxide, ether, and oxygen. Tubocurarine was given to obtain relaxation. Both adrenal glands were removed at the same operation in five patients, but in the sixth, because of her poor general condition, the adrenalectomy was carried out in two stages, with an interval of 21 days between each. A posterolateral incision was made through the bed of the 12th rib, with the patient in the lateral position. The right adrenal gland was always resected first, owing to its greater inaccessibility and its proximity to the inferior vena cava. The kidneys were examined and the adherence of their capsules was noted. Wedge biopsies were taken from both. During the operation normal saline was given intravenously, and blood was substituted if necessary. Two patients were given noradrenaline intravenously towards the end of the operation, in order to maintain a systolic blood-pressure of 140 or more. None received corticoids intravenously during the operation, but 50 to 100 mg. of cortisone was given orally later that day to all patients but one. Thereafter the dose varied considerably, but was reduced to 50 mg. daily, or less, as rapidly as it was thought that the patient's condition would permit, usually by the fifth to the seventh day after adrenalectomy.

Pathological Findings

The gross appearance and histological findings in the kidneys, together with the outcome, are summarized in Table III. The kidneys in two of the three survivors, and in one of the patients who died, appeared normal in size, the capsule stripped easily, and the cortex was not scarred. In the other survivor both

TABLE III

Pathological Features of Kidneys

Case number	*Macroscopic*	*Microscopic (biopsy)*	*Pathological diagnosis*	*Outcome*
	At autopsy			
1	Right: 180 gm. Normal size. Cortex smooth, and capsule strips easily Left: 200 gm. Normal size. Cortex smooth, and capsule strips easily	Many arterioles show fibrinoid necrosis. Glomerular changes include capsular thickening, with occasional hyalinization or necrosis of glomerular tuft	Malignant nephrosclerosis	Died 53rd day
	At operation			
2	Both normal in size. Capsule strips easily. Cortex slightly granular	Blood-vessels show severe arteriosclerotic change, with marked intimal hyperplasia but no fibrinoid necrosis. Glomeruli show increased cellularity, capsular adhesions, and in places complete fibrous replacement	Severe nephrosclerosis	Alive at 900 days
	At operation			
3	Both small. No patchy atrophy or cortical scars seen. Cortex smooth; capsule strips easily	Arterioles show marked hyalinization and intimal hyperplasia, but no frank fibrinoid necrosis. The glomeruli show thickening of the capsular and capillary basement membranes, and varying degrees of sclerosis and atrophy	Severe nephrosclerosis	Alive at 750 days
	At autopsy			
4	Right: 90 gm. Small, with slightly adherent capsule; cortex thin Left: 155 gm. Small, with slightly adherent capsule; cortex thin	Severe arteriosclerosis of vessels, with occasional areas of fibrinoid necrosis. Ve. " advanced fibrosis and hyalinization of glomeruli	Malignant nephrosclerosis	Died 36 hrs.
	At autopsy			
5	Right: 130 gm. Small. Cortex slightly granular, with adherent capsule Left: 150 gm. Small. Cortex slightly granular, with adherent capsule	Arterioles show marked fibrinoid necrosis, with glomerular hyalinization and occasional areas of haemorrhage	Malignant nephrosclerosis	Died 6th day
	At operation			
6	Both normal in size. Capsules slightly adherent, and surface slightly granular	Blood-vessels are markedly arteriosclerotic. Glomeruli show increased cellularity and sclerosis. Tubules contain colloid casts. No arteriolar fibrinoid necrosis	Severe nephrosclerosis	Alive at 550 days

kidneys appeared to be rather small, but were otherwise normal, and in two patients who died both kidneys were small, the capsules adherent, and the cortex granular in appearance. In all cases there was histological evidence of severe renal damage. The three patients who died had malignant nephrosclerosis. In the three survivors the histological changes were similar except for the absence of the arteriolar fibrinoid change, and have been called severe nephrosclerosis. The histological findings correlate well with the severity of the hypertensive disease. All three patients with malignant nephrosclerosis had severe retinopathy and proteinuria of more than 0·5 gm. per day. Of the three patients with severe nephrosclerosis, only one had retinal haemorrhages and exudates, and the proteinuria in all three was less than 0·5 gm. per day. The weight of the adrenal

glands was within normal limits (5 to 10 gm.) in all patients. Microscopy of serial sections failed to demonstrate any abnormality, and the amount and distribution of sudanophile lipid in the adrenal cortex were normal. The medulla was normal in all cases.

Results

Three patients died within eight weeks of operation. The blood-pressure of one patient (Case 4) fell precipitously at operation, and never recovered in spite of transfusions; he died 36 hours later. The second died on the sixth day after operation from acute left ventricular failure precipitated by a steadily rising blood-pressure, which it is thought may have been due to overdosage with cortisone. The third patient died suddenly from cerebral thrombosis on the 53rd day after operation. At the time of her death her blood-pressure had been greatly reduced, and she was due to go home.

Immediately after operation all the survivors showed variable changes in blood-pressure, which are detailed in Figs. 1 to 4. The pressure always fell at operation, but returned to previous levels within five days. After a further period of one to 10 days it again began to fall, and reached a lower stable level during the next 10 days. The height to which it rose after the operation, and the length of time it maintained this level, varied directly with the total amount of cortisone given during this period. The patient who died on the sixth day after operation (Case 5) was given 1 gm. of cortisone during this time, and his blood-pressure rose progressively to above the maximum level found before operation. Another patient (Case 1) was given 900 mg. of cortisone over a similar period, and her blood-pressure returned to, and was maintained at, its previous levels for two weeks after operation (Fig. 1). Two others (Cases 3 and 6) received 725 and 675 mg. respectively over a similar period, and showed a less sustained rise in blood-pressure (Figs. 3 and 4). One patient (Case 2) received only 425 mg. of cortisone during this time; her blood-pressure never reached the previous levels, and fell most rapidly afterwards (Fig. 2). None failed to show a substantial fall in blood-pressure when the dosage of cortisone was reduced sufficiently. The headache disappeared in all patients after the blood-pressure fell. Blurring of vision improved less rapidly, and was closely related to the appearance of the retinae. Both papilloedema and subjective visual disturbances disappeared within three weeks after a substantial fall in blood-pressure had occurred. Symptoms due to cardiac failure were much slower to improve. The three patients who complained of severe dyspnoea on exertion experienced little relief of this symptom, and none showed much increase in capacity for exercise up to the 50th day after operation. The patient who had orthopnoea on admission was relieved completely by the 30th day after operation. None showed any change in the size of the heart during this early period.

Reduction in the dosage of cortisone was accompanied in all cases by a considerable sodium diuresis, of from 300 to 750 mEq., and followed by the appearance of biochemical changes consistent with mild adrenocortical insufficiency, with a

low level of serum-sodium and increased potassium and urea. The rise in the urea level was the most sensitive index of adrenocortical insufficiency. The potassium balances in all patients, and the nitrogen balances in the two in whom it was estimated, were negative in the period immediately following operation (Figs. 3 and 4). The reduction in dosage of cortisone was accompanied in all cases

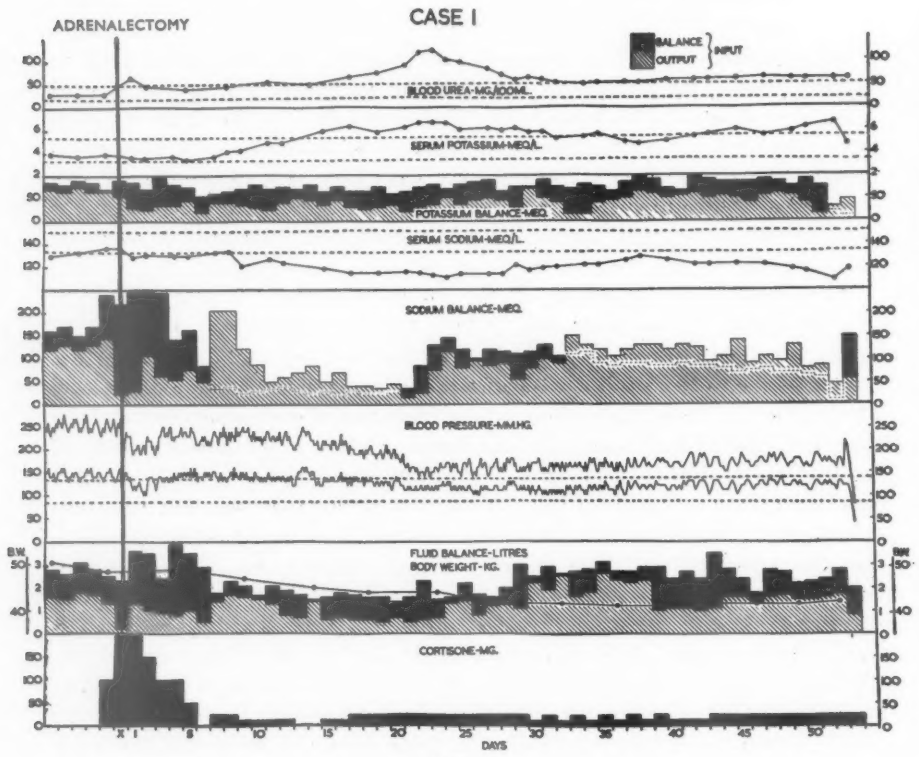

FIG. 1

by a fall in body-weight of from 6 to 10 kg., and an accompanying loss of body-water. Any subsequent increase in the dosage of cortisone invariably caused a return of the serum electrolytes and urea to normal levels, after a time-lag which varied with the dosage, but was accompanied by a rise in blood-pressure. Daily estimations of the excretion of the urinary 17-ketosteroids were made in two female patients of similar weight and nutritional status, but the results differed widely (Figs. 3 and 4). In one the reduction of oral cortisone to 50 mg. daily resulted in the disappearance of 17-ketosteroids from the urine, and they reappeared only when the dosage was increased to 75 mg. In the other a daily intake of 50 mg. of cortisone was associated with the excretion of 17-ketosteroids in an amount equal to twice that excreted daily during the control period.

Three patients have now been observed for more than 900, 750, and 550 days

respectively since operation (Figs. 5, 6, and 7). On leaving hospital they were advised to live normal lives, without restriction of diet or activities, but to adhere to the prescribed dose of cortisone. They, their close relatives, and the family doctor were advised that should a severe intercurrent illness or accident

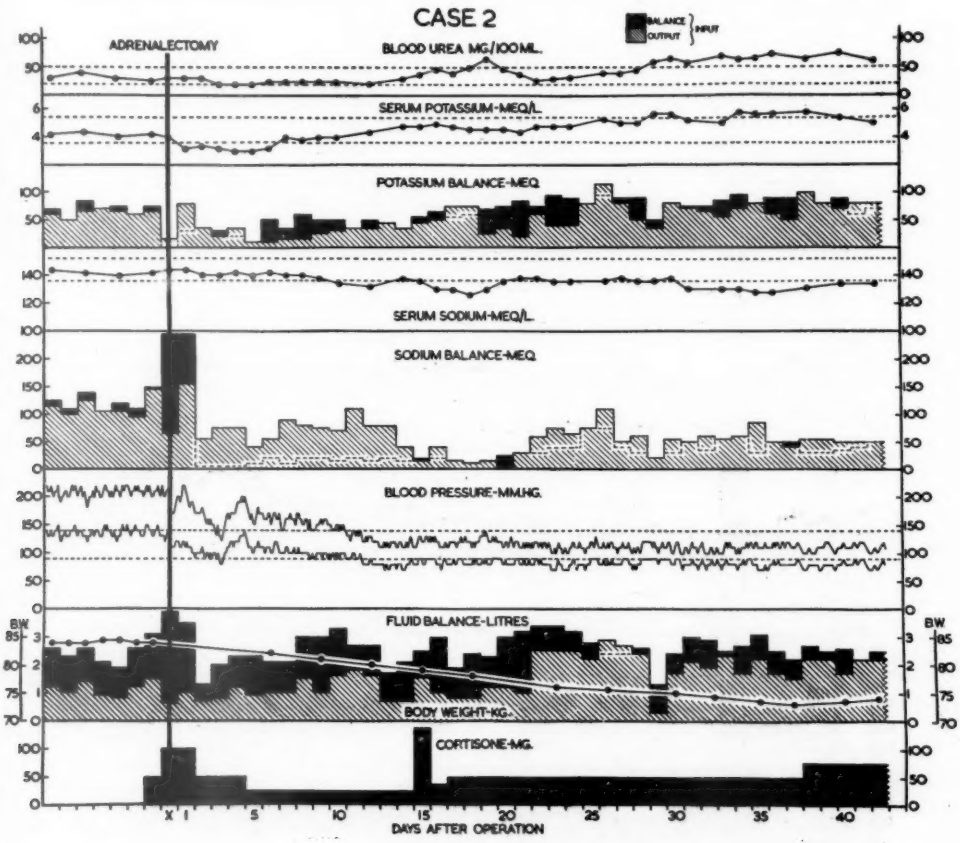

FIG. 2

FIGS. 1 and 2. Cases 1 and 2. Cortisone dosage, blood-pressure, the balances of fluid, sodium, and potassium (positive balance shown in black). The serum values of sodium, potassium, and urea, and body-weight before and after operation.

befall, 500 mg. of cortisone should be taken and the patient referred immediately to the Medical Unit. Within a few weeks of their discharge from hospital all three developed headache, papilloedema, and proteinuria, with a return of the arterial hypertension, and the serum-electrolytes and urea returned to normal values. They had been having from 50 to 100 mg. of cortisone daily during this period. The symptoms and signs disappeared when the dosage was reduced to 50 mg. or below, and the level of the serum-electrolytes again indicated mild adrenocortical insufficiency. In two patients the symptoms and hypertension have recurred on

two occasions, each of which was associated with an increase in the dosage of cortisone. They invariably resolved when it was reduced, but there was generally a lapse of two to three weeks between any change in dosage and the establishment of a new level of blood-pressure. Since discharge from hospital all three survivors have shown a considerable increase in their capacity for exercise, the greatest

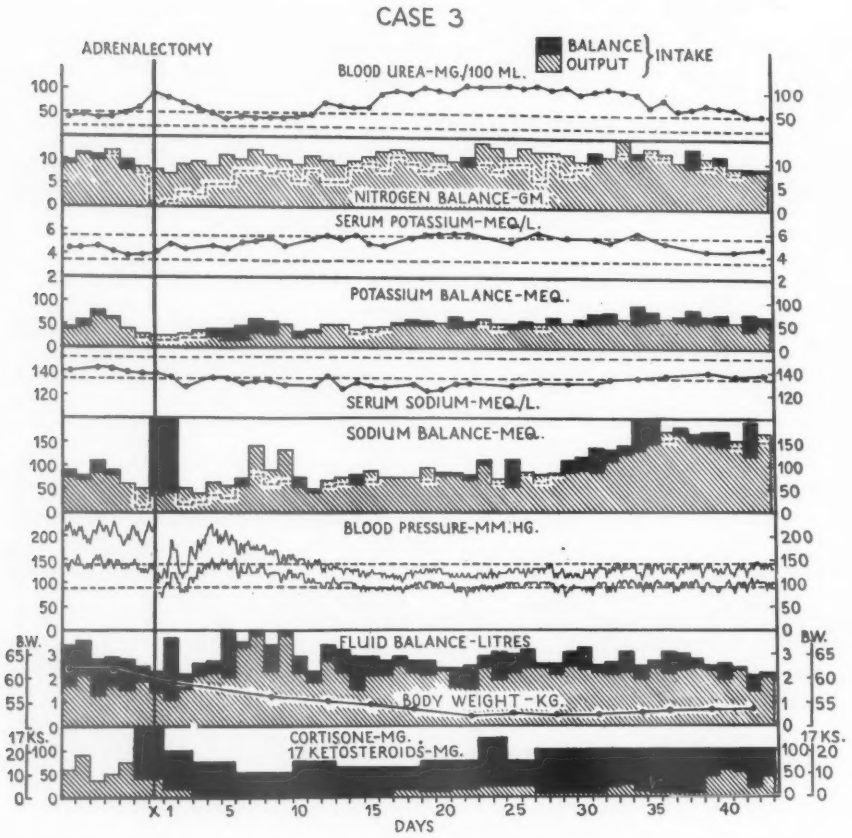

FIG. 3

FIGS. 3 and 4. Cases 3 and 6. Cortisone dosage balanced with 17-ketosteroid excretion; blood-pressure, the balances of fluid, sodium, potassium, and nitrogen (positive balances shown in black), and the serum values of sodium, potassium, and urea (with normal limits shown by interrupted lines) and body-weight before and after operation.

increase being in those patients who have survived longest. In all the heart has returned to normal size, and the electrocardiograph has also reverted to normal (Plate 45, Fig. 8). Renal function has not deteriorated in any patient since operation. The proteinuria and cylindruria, which disappeared shortly after the blood-pressure became normal, reappeared only when it rose again with an excessive dosage of cortisone. The concentrating power of the kidney has not

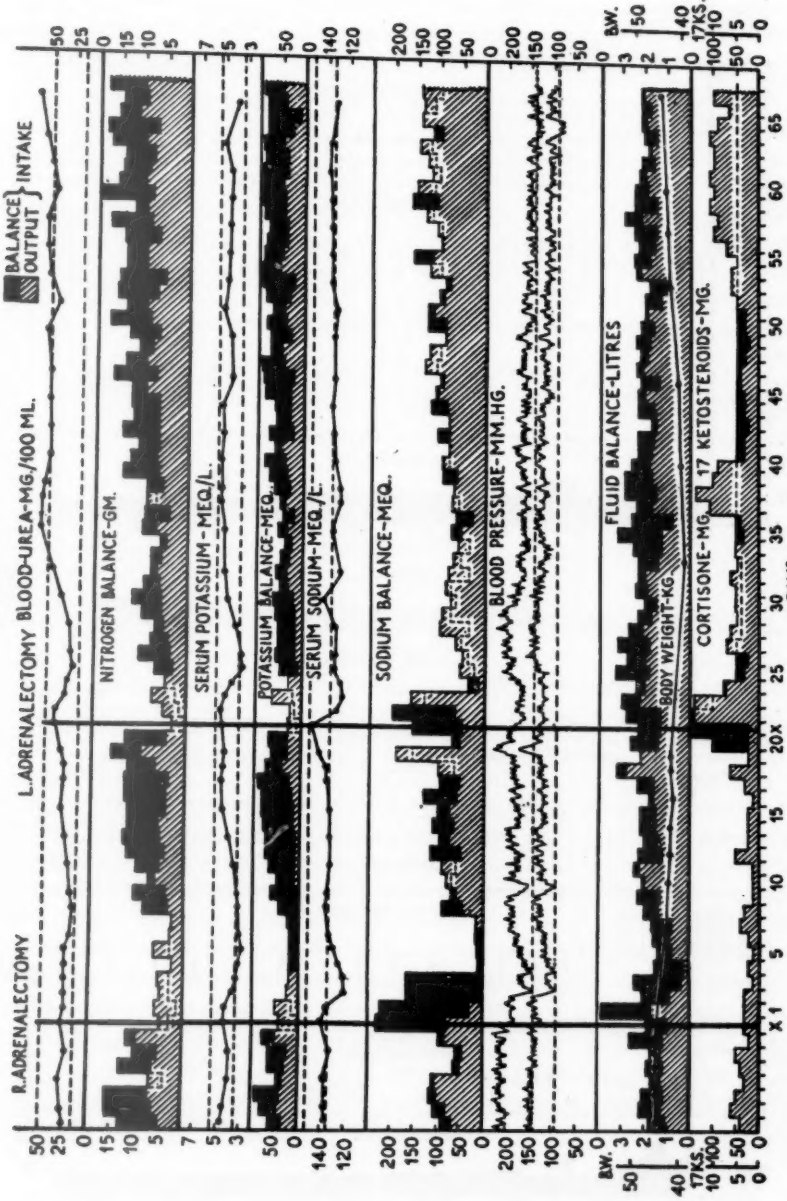
CASE 6
R.ADRENALECTOMY
L.ADRENALECTOMY
BLOOD-UREA-MG./100 ML.
BALANCE
OUTPUT
INTAKE
NITROGEN BALANCE-GM.
SERUM POTASSIUM-MEQ./L.
POTASSIUM BALANCE-MEQ.
SERUM SODIUM-MEQ./L.
SODIUM BALANCE-MEQ.
BLOOD PRESSURE-MM.HG.
FLUID BALANCE-LITRES
BODY WEIGHT-KG.
CORTISONE-MG.
17 KETOSTEROIDS-MG.
BW.
17KS.
X 1
5
10
15
20X
25
30
35
40
45
50
55
60
65
DAYS

FIG. 4

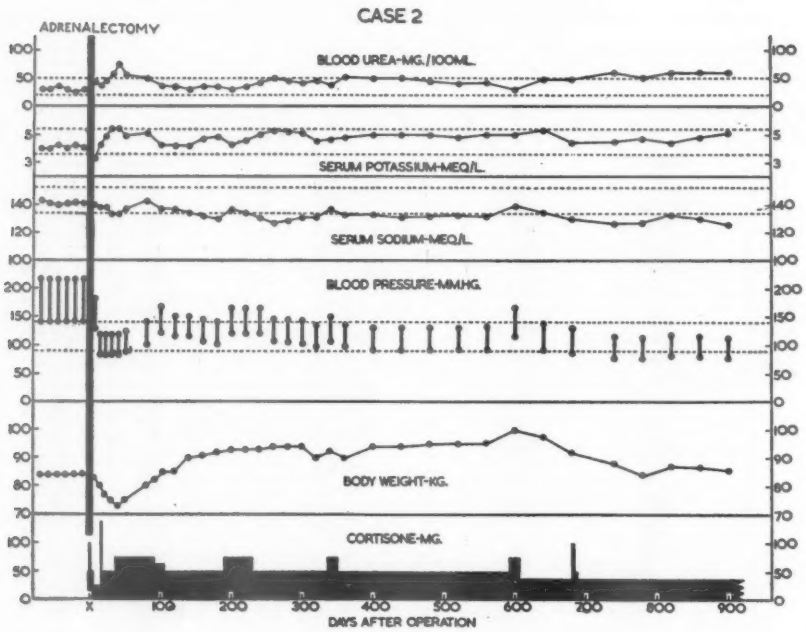
CASE 2
ADRENALECTOMY
BLOOD UREA-MG./100ML.
SERUM POTASSIUM-MEQ/L.
SERUM SODIUM-MEQ/L.
BLOOD PRESSURE-MM.HG.
BODY WEIGHT-KG.
CORTISONE-MG.
X
100
200
300
400
500
600
700
800
900
DAYS AFTER OPERATION

FIG. 5

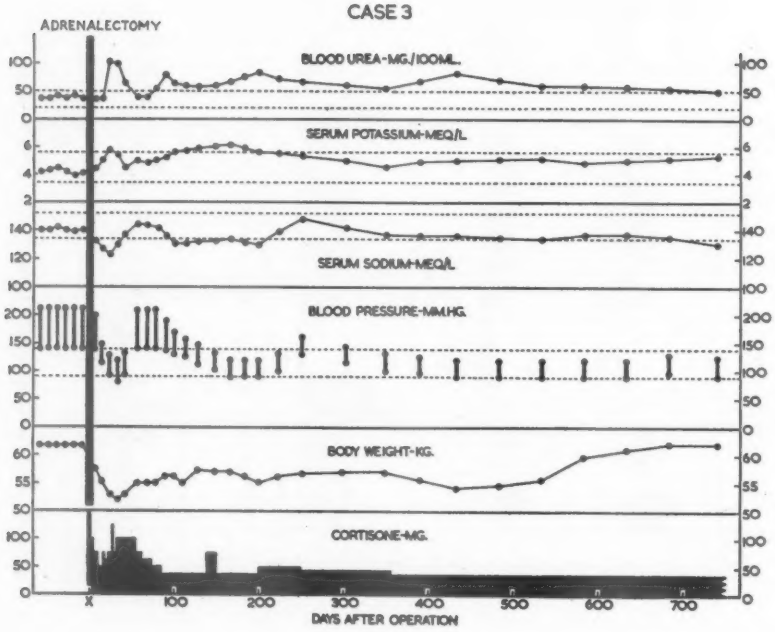
CASE 3
ADRENALECTOMY
BLOOD UREA-MG./100ML.
SERUM POTASSIUM-MEQ/L.
SERUM SODIUM-MEQ/L.
BLOOD PRESSURE-MM.HG.
BODY WEIGHT-KG.
CORTISONE-MG.
X
100
200
300
400
500
600
700
DAYS AFTER OPERATION

FIG. 6

diminished in any of the patients, and the creatinine clearance in one (Case 3), which was reduced to 53 ml. per minute before operation, has remained unchanged. Before operation the menstrual cycle was normal in all patients. It ceased at operation, but returned two months later, and has since remained normal.

At the present time the three survivors are well and leading active lives. All

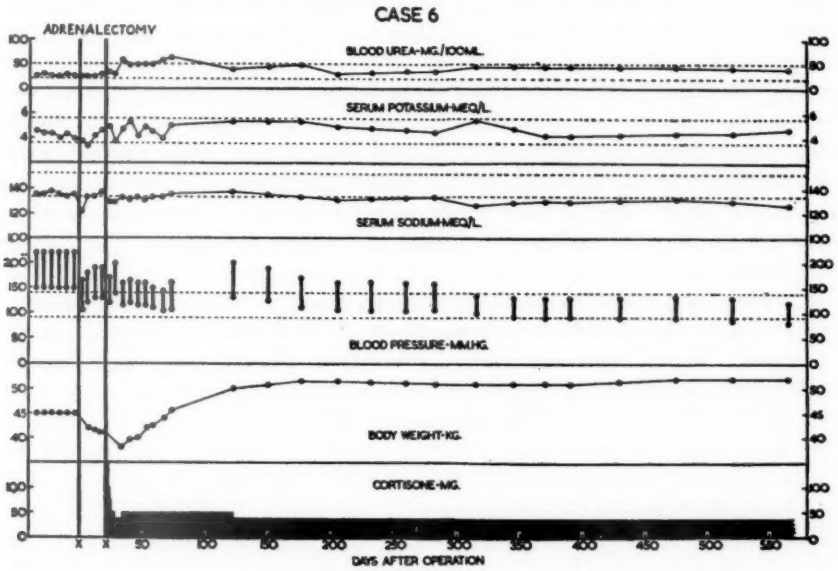

FIG. 7

FIGS. 5, 6, and 7. Cases 2, 3, and 6. Cortisone dosage, blood-pressure, and the serum values of sodium, potassium, and urea (with normal limits shown by interrupted lines), and body-weight before and after operation.

are now receiving a total dose of 37·5 mg. of cortisone daily by mouth, are free from headache and disturbances of vision, and have an increased capacity for exercise. In all three the blood-pressure is normal and the heart has reverted to normal, and none show retinal changes or proteinuria. The only symptom which might indicate adrenocortical insufficiency is slight blunting of the appetite, but all have maintained or increased their weight. The level of the serum-electrolytes and urea also suggests, however, slight adrenocortical insufficiency. The blood picture has remained normal, and no changes have been observed in the proteins, lipids, phosphorus, or alkaline phosphatase in the serum, but two of the three survivors show a slight persistent hypercalcaemia which is unexplained. Both have experienced a variable amount of pain, which may be referred to bone, and this problem is being investigated.

Discussion

The heavy mortality in this small group of patients treated by bilateral adrenalectomy is not surprising in view of the very advanced stage of the

hypertensive disease at the time of operation. The survivors are in a satisfactory state; two have now lived for more than two years, and another for 18 months, since operation. They are free from symptoms, and able to lead normal active lives, whereas previously they were severely incapacitated, and it had been considered unlikely that any would survive for more than a year. The persistent reduction in blood-pressure has caused a significant reduction in size of the heart, resolution of the papilloedema, retinal haemorrhages, and exudates, and disappearance of the proteinuria. It was feared that renal function, which was impaired before operation, would get worse, but tests of renal capacity to concentrate urine show no such deterioration. It is possible, therefore, that the disease has been retarded, or perhaps even arrested, by a state of slight adrenocortical insufficiency; but it appears that the liability to excessive constriction of the arteriolar vascular bed, which is fundamental to essential hypertension, persists, and that a slight increase in the dosage of cortisone quickly recalls a severe hypertensive state.

The experience of others, that hypertension may persist after adrenalectomy, may be due to the use of larger doses of cortisone, but other factors may also be involved. Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt (1952) and van't Hoff (1957) have reported that total adrenalectomy may cause no significant fall in blood-pressure in patients with severe hypertension, in spite of the excretion of large amounts of sodium and the reduction of oedema. In the series reported by Thorn and his colleagues (1952) this lack of response appears to have been related to the extent of renal involvement. In the present series the renal damage in the patient (Case 1) whose blood-pressure failed to reach normal levels was more severe than in any of the three patients in whom the blood-pressure returned to normal after adrenalectomy. The vascular damage associated with essential hypertension injures the kidney progressively, and it is likely, therefore, that mild adrenocortical insufficiency may relieve the hypertension before severe renal damage has occurred, but may fail to do so later. These results would be expected from work on animals, since adrenalectomy does not abolish the hypertension associated with the nephritis caused by kaolin in dogs (Jeffers, Lindauer, and Lukens, 1937–8) or by nephrotoxic globulin in rats (Knowlton, Stoerk, Seegal, and Loeb, 1946) but does so in the Goldblatt animal, in which it is presumed little secondary renal damage has occurred.

The parts played by the renal pressor factor and by the adrenal cortex in hypertension are manifestly different, and probably unrelated. From the experimental work reviewed earlier, and from the data recorded in this paper, it seems likely that the adrenal cortex exerts its influence on essential hypertension mainly through its action on the sodium ion, since the concentration of this ion alone is altered significantly in relation to the level of the blood-pressure. The manner in which the sodium ion influences blood-pressure is, however, not clear. It may act by altering the volume of the plasma, or more directly at the level of the cell. Although the reduction of plasma volume in Addison's disease may be severe, there are no data regarding the plasma volume in hypertensive patients treated by adrenalectomy and maintained with an adequate dosage of cortisone.

Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt (1952) stated that the plasma volume had been measured in their patients, but gave no results, and no measurements were made in the patients described in the present paper. It seems unlikely, however, that the reduction in blood-pressure is due entirely to this factor, since the four patients whose hearts were catheterized showed no change in systemic blood-pressure after 300 to 400 ml. of blood were removed. Even less is known about the action of the sodium ion at cell level, but it is likely that the muscular hypotonia and profound weakness associated with Addison's disease are a result of an alteration in the ratio of the concentrations of intra- and extracellular sodium and potassium ions. This change must affect not only the cells of striated muscles, but all cells throughout the body, including the smooth muscle of the vascular system, and may well be responsible for the vascular hypotonia observed in our patients after adrenalectomy. Whatever the explanation may be, bilateral adrenalectomy alone has effectively reduced the blood-pressure in these four patients. It is not a method of treatment to be employed, however, unless medical measures have failed to terminate the malignant phase of the disease, and it should never be attempted in the presence of frank renal failure.

The substance of this paper was read before a meeting of the Endocrine Section of the Royal Society of Medicine on January 24, 1956. Part of the study was made during the tenure of a Medical Research Council Fellowship in Clinical Research by one of the authors (S. H. T.). The authors wish to thank Dr. John Gillhespy and Dr. Wakes Miller for referring Cases 1 and 3 respectively, and to express their gratitude to Miss E. Richards for her assistance with the balance studies, to Mr. Garfield Thomas for the biochemical analyses, and to Mr. T. F. Dee for reproduction of radiographs and clinical photography.

APPENDIX

Case 1. R. W., a housewife aged 39 years with three children, was admitted to hospital on 10.1.54. She gave no family history of hypertension. Two years before admission severe arterial hypertension was found during a routine antenatal examination, but she had no symptoms. This pregnancy, and one six months before admission, ended in spontaneous abortions. Eighteen months before admission she first began to have increasing dyspnoea on exertion, and 12 months before admission symptoms suggestive of an acute coronary occlusion. Subsequently she was treated with oral hexamethonium in another hospital, but a few weeks later began to suffer from increasingly severe headache and blurred vision. On admission she was breathless at rest, and had orthopnoea and swelling of the ankles. Her pulse was regular at 90 beats per minute, and her blood-pressure 270–230/160–130. Her heart was much enlarged, and a radiograph of the chest and electrocardiogram showed left ventricular hypertrophy and preponderance respectively. There was no venous distension or oedema of the legs, but numerous fine râles were audible at both lung bases. She had severe papilloedema, with retinal exudates and haemorrhages. The urine contained erythrocytes and granular casts, and 0·5 to 1·0 gm. of protein per day, and was sterile. After deprivation of water for 12 hours the specific gravity was 1,024. The blood-urea was 28 mg. per 100 ml., and an intravenous pyelogram was normal. The blood count, erythrocyte sedimentation rate, and serum values for sodium,

potassium, chloride, calcium, phosphorus, alkaline phosphatase, albumin, globulin, and lipids were normal. The benzodioxane test was negative. The daily excretion of urinary 17-ketosteroids gave a mean value of 12 mg. in 24 hours. Her blood-pressure was unchanged after four weeks' rest in hospital, and both adrenal glands were removed on 15.2.54. They were normal in size and weight, and showed no abnormal histological features. Histological examination of sections of both kidneys, obtained by biopsy, showed the presence of severe arteriosclerosis with fibrinoid arteriolar changes. The patient was given 100 mg. of cortisone orally on the day before operation, 200 mg. on the day of operation, and after operation 200 mg. on the first day, 150 mg. on the second day, 100 mg. daily on the third and fourth days, and 50 mg. on the fifth day. She was given no cortisone on the sixth day, 25 mg. daily on the seventh and eighth days, and then 12·5 mg. daily for the next four days. She received no cortisone on the 13th and 14th days, 12·5 mg. daily on the 15th and 16th days, and then 25 mg. daily for the next two weeks. She then had 25 mg. and 12·5 mg. alternately for two weeks, and subsequently 25 mg. daily. There was a transient fall in her blood-pressure immediately after operation, but it rose to 250–210/150–130 by the third day. After the fourth day there was a considerable loss of weight, and 750 mEq. of sodium were lost in the urine during the next two weeks. The level of serum-sodium fell, and that of serum-potassium and urea rose beyond the normal limits. The blood-pressure remained high until the end of the second week, when it fell gradually to 180–140/130–100 at the end of the third week, and weakness, anorexia, and nausea developed. These symptoms disappeared when 5 gm. of sodium were given orally each day, without change in the dosage of cortisone. The level of the serum-electrolytes and urea returned to normal, and her blood-pressure did not alter. During the next 30 days she continued to have 5 gm. of sodium chloride orally by mouth. By the fourth week after operation she had no headache, and was much less breathless. Her orthopnoea disappeared, and by the seventh week she was able to walk on the level without breathlessness. Her vision was normal, and the papilloedema disappeared. The excretion of urinary protein fell to 0·2 gm. per 24 hours, and she was still able to concentrate urine to a specific gravity of 1,024. She had a slight loss of appetite, and her weight, which was now constant, was 42 kg., compared with 50 kg. before operation. Slight diffuse brown pigmentation of the skin and buccal mucosae was observed, and the level of her serum-sodium was at the lower limit of normal, and that of potassium and urea at the upper limit of normal, six weeks after operation. At the end of the seventh week, and the day before she was due to be sent home, she suddenly became unconscious, with signs of a brain-stem lesion; she died 40 hours later, on the 53rd day after her operation, without regaining consciousness.

Autopsy report (E. N. 125/54). The cause of death was infarction of the brain-stem involving the pons and medulla and, although the vessel responsible was not defined, all the cerebral vessels showed very severe atheromatous changes. The heart weighed 610 gm., and there was gross left ventricular hypertrophy. The coronary arteries showed severe atheroma, but there was no evidence of myocardial infarction. The aorta was the site of an old dissecting aneurysm extending from a transverse tear in the ascending arch down to the iliac arteries. The dissection did not extend along any of the other major vessels, but the origin of the renal arteries was narrowed. The kidneys were normal in size, and additional histological sections confirmed the observations on the sections taken at biopsy. The pituitary and thyroid glands were normal, and no adrenal remnants were found.

Case 2. D. S., a married housewife, aged 41 years, who has three children,

was admitted to hospital on 19.3.54. Both her parents died of hypertension, and two of her sisters have high blood-pressure. For 12 years the patient had been known to have hypertension with headache, and two years before admission she had been forced to give up her work as a canteen waitress. A year later she developed increasing breathlessness on exertion. She had previously been in hospital in 1953 with essential hypertension, and was then given hexamethonium parenterally, but she was intolerant of the side-effects of the drug. On admission in 1954 her blood-pressure was labile, with a range of 250–190/160–120 mm. Hg, and her pulse was regular at 80 beats per minute. Her heart was enlarged, and a radiograph of her chest and an electrocardiogram showed considerable left ventricular hypertrophy and preponderance respectively. All peripheral pulses were palpable. Mild papilloedema was present in both eyes, but no exudates or haemorrhages were seen. The urine contained no cells, occasional granular casts, and 0·5 to 0·1 gm. of protein per 24 hours, and was sterile. When deprived of fluids for 12 hours she concentrated her urine to a specific gravity of 1,022. Her blood-urea was 20–40 mg./100 ml., and an intravenous pyelogram was normal. Her blood count, erythrocyte sedimentation rate, and the serum values for sodium, potassium, chloride, albumin, globulin, calcium, phosphorus, alkaline phosphatase, and lipids were normal. The benzodioxane test was negative. The mean value for excretion of 17-ketosteroids in urine was 10 mg. in 24 hours. Her blood-pressure was largely unchanged after four weeks' rest in hospital, and both adrenal glands were removed on 21.4.54. They were normal in size and weight, and showed no abnormal histological features. Histological examination of sections of both kidneys, obtained by biopsy, showed severe arteriosclerosis without fibrinoid arteriolonecrosis. The patient was given 50 gm. of cortisone orally the day before operation, 100 mg. on the day of operation and on the following day, 50 mg. daily on the succeeding three days, and 25 mg. daily thereafter. Her blood-pressure fell during operation, but had returned to its previous level on the next day. It fell to 140/90 on the third day, but returned to 190/130 on the fifth day. It then fell gradually to 120–101/90–80 during the next week, and remained at this level until she was discharged from hospital. She lost weight throughout this period, and this change was associated with the loss of 500 mEq. of sodium. Immediately after the operation her potassium balance was negative, but it was normal thereafter. By the third week after operation the serum-sodium level fell below normal, that of serum-potassium rose to the upper limit of normal, and the blood-urea increased to above normal levels. She developed mild anorexia, and was given 137·5 mg. of cortisone for one day and 50 mg. daily for the next 20 days, but the level of her serum-electrolytes and blood-pressure did not alter significantly. The dose was therefore increased to 75 mg. daily, and she was sent home on the 42nd day after operation. She felt well except for some breathlessness on exertion. The headache, papilloedema, and proteinuria had disappeared, and she weighed 73 kg., having lost 10 kg.

After discharge from hospital her blood-pressure rose to 170/120, and the headache, papilloedema, and proteinuria returned. She had had 75 mg. of cortisone daily for 50 days, but it was then reduced to 50 mg. daily, and was kept at this level for the next 500 days, except for two short spells when she had mild infections of the upper respiratory tract. Her blood-pressure fell gradually, and the headache, papilloedema, and proteinuria disappeared again. The serum-sodium remained at the lower limit of normal, and the serum-potassium and urea were at the upper limits of normal. On about the 600th day after her operation she increased her dose of cortisone; her blood-pressure rose, and the levels of sodium, potassium, and urea in the serum returned to the middle of the normal

range. The dosage of cortisone was then reduced to 37·5 mg. daily; the blood-pressure fell to normal, the serum-sodium level fell, and the serum-potassium and urea rose to their previous levels again.

At the present time, 900 days after operation, she feels well, and has no symptoms except slight breathlessness on exertion and impairment of appetite. Her weight is 100 kg. and constant, and she is able to lead a full and active life, looking after her family and working part-time in a factory. Her menstrual cycle, which was normal before, was re-established two months after operation, and has remained regular since. Her blood-pressure is normal, and she has no papilloedema or proteinuria. Her heart is of normal size, and a radiograph of her chest and electrocardiogram now show no evidence of left ventricular hypertrophy or preponderance. Her renal function has not deteriorated, and she can concentrate urine to a specific gravity of 1,024. The serum-electrolytes, blood count, and erythrocyte sedimentation rate have not changed, except that the serum-calcium has increased intermittently from 10·6 to 11·7 mg. per 100 ml. during the past six months, and this increase has been associated on three occasions with transient but severe cervical vertebral pain. The phosphorus and alkaline phosphatase levels in the blood have always been normal.

Case 3. M. S. a married housewife aged 26 years, without children, who worked as a private secretary, was admitted to hospital on 13.8.54. Her mother had hypertension, but no other members of the family are known to have been affected. The patient first began to have headache seven years, and breathlessness on exertion two years, before admission. Six months before admission she had an attack of hypertensive encephalopathy, lasting three days, which left no neurological signs. Two months before admission her vision became blurred, and deteriorated rapidly, causing her to stop work. On admission her blood-pressure was 250–200/170–140, and her pulse was regular but labile at 80 to 120 beats per minute. Her heart was moderately enlarged, and a radiograph of her chest and electrocardiogram showed left ventricular hypertrophy and preponderance respectively. All peripheral pulses were present. She had severe bilateral papilloedema, but no retinal exudates or haemorrhages. Her urine contained small numbers of erythrocytes, no leucocytes, numerous granular and hyaline casts, and 0·4 to 0·5 gm. of protein per 24 hours. It was sterile. She was able to concentrate urine to a specific gravity of 1,020 after 12 hours without fluids, but the creatinine clearance was reduced to 53 ml. per minute. Her blood-urea was 39 mg. per 100 ml. An intravenous pyelogram showed small kidneys which excreted the dye slowly. Her blood count, erythrocyte sedimentation rate, and the serum values for sodium, potassium, chloride, albumin, globulin, calcium, phosphorus, alkaline phosphatase, and lipids were normal. The benzodioxane test was negative. The mean value for the excretion of urinary 17-ketosteroids was 10 mg. in 24 hours. Her heart was catheterized, and the resting pressure in the right atrium was 4 mm. Hg, in the right ventricle 20/5 mm. Hg, and in the pulmonary artery 25/15 mm. Hg; the pulmonary capillary pressure was 9 mm. Hg. After five minutes' exercise the pulmonary artery pressure rose to 55/45 mm. Hg and the brachial artery pressure rose from 200/146 at rest to 230/155. At rest the consumption of oxygen was 126 ml. per minute per sq. m., and the cardiac output was 3·06 l. per minute per sq. m. After five minutes' exercise the consumption of oxygen rose to 635 ml. per minute per sq. m., and the cardiac output to 6·62 l. per minute per sq. m. Her systemic blood-pressure fell to 220–170/160–130 after three weeks' rest in hospital. Treatment with 3 mg. reserpine and 300 mg. hydrallazine daily did not affect it or reduce her symptoms, and she developed a rash suggestive of systemic lupus erythematosus, accompanied by fever. Treatment was discontinued, and the

fever and rash subsided rapidly. Both adrenal glands were removed on 7.10.54. They were normal in size and weight, and showed no abnormal histological features. Histological examination of sections of the kidneys, removed by biopsy, showed severe arteriosclerosis without fibrinoid arteriolar changes. The patient was given 150 mg. of cortisone orally on the day before and on the day of operation, 100 mg. daily for the next two days, 75 mg. daily for the next three days, and then 50 mg. daily until the 10th day, when it was increased to 75 mg. Her blood-pressure fell during the operation, but returned to the previous level on the fourth day after operation. It then fell slowly to 140–110/100–80 in the third week. Her loss of weight was accompanied by a moderate sodium diuresis of 360 mEq. The potassium balance was negative immediately after the operation, but was subsequently normal. The nitrogen balance was negative for longer, and returned to normal more slowly. Six days after the operation the dosage of cortisone was reduced to 50 mg. daily. Anorexia developed rapidly, and the patient felt weak; there was an increase in the excretion of sodium in her urine, a fall in the level of serum-sodium, and an increase of serum-potassium and urea. The excretion of 17-ketosteroids in the urine ceased. The dosage of cortisone was increased, first to 75 mg. and later to 100 mg. daily. She was sent home after taking 100 mg. daily for 16 days. She felt well, and had no symptoms except for some breathlessness on exertion; her papilloedema and proteinuria had disappeared, and she weighed 53 kg., having lost 10 kg. since operation. Her blood-pressure and the level of her serum-electrolytes were normal, she was in positive sodium, potassium, and nitrogen balance, and the excretion of 17-ketosteroids was normal.

Ten days after she returned home her blood-pressure was 210/140, but she had no papilloedema. The dosage of cortisone was reduced to 37·5 mg. daily, but four weeks later her blood-pressure was still high and papilloedema and proteinuria had reappeared, although the serum-sodium level had fallen below and that of serum-potassium and urea had risen above the normal range. Twelve weeks after the dose had been reduced to 37·5 mg. daily her blood-pressure had returned to normal, and the papilloedema and proteinuria had disappeared again. Between the 200th and 250th day after the operation she increased the dose to 50 mg. daily because of an infection of the upper respiratory tract. Her headache returned, and her blood-pressure rose to 170/130, but she had no papilloedema or proteinuria. The serum-sodium and potassium returned to normal levels, but the level of blood-urea remained above normal. The dosage of cortisone was then reduced to 43 mg., and 100 days later to 37·5 mg. daily; her symptoms disappeared, and her blood-pressure became normal, but the serum-sodium fell again to the lower limit of normal. Six months after the operation she began to suffer from intermittent aching pains in both legs. There were no abnormal physical signs, and radiographs revealed no bony lesion. The serum-calcium was 12 mg. per 100 ml., but the serum phosphorus and alkaline phosphatase were normal. These pains have continued since, with remissions and exacerbations, and are relieved by analgesics.

At the present time, 750 days after operation, she feels well, and has no other symptoms except for slight breathlessness on exertion. She is leading a full and active life, and has been working full-time as a secretary since her discharge from hospital. Her blood-pressure is normal, and she has no papilloedema or proteinuria. Her weight is 53 kg. Her heart has reverted to normal size, and the electrocardiogram is now normal. Her renal function has not deteriorated; she is able to concentrate urine to a specific gravity of 1,023, and creatinine clearance is unchanged at 50 ml. per minute. Her menstrual cycle, which was normal before operation, was re-established two months after, and has been regular

since. Her serum-electrolyte levels, blood count, and erythrocyte sedimentation rate have not changed.

Case 4. L. H., a married man aged 37 years, who had one child and worked as a salesman, was admitted to hospital on 26.8.54. He gave no family history of high blood-pressure. For nine months he had had headache, dyspnoea on exertion, orthopnoea, and blurred vision, associated with hypertension. Treatment with oral hexamethonium by his family doctor produced no remission of symptoms or fall in blood-pressure. On admission his blood-pressure was 240–200/170–130, and his pulse was regular at 88 beats per minute. His heart was considerably enlarged, and a radiograph of the chest and electrocardiogram showed gross left ventricular hypertrophy and preponderance respectively. He had no venous distension or oedema of the legs, but scattered fine râles were present at both lung bases. All peripheral pulses were present. Severe papilloedema and retinal exudates and haemorrhages were seen in both optic fundi. His urine contained a few erythrocytes and granular casts, and 0·5 to 0·75 gm. of protein per 24 hours, and was sterile. He was able to concentrate urine to a specific gravity of 1,021 after 12 hours without water, but the creatinine clearance was reduced to 62 ml. per minute and his blood-urea was 56–69 mg. per 100 ml. An intravenous pyelogram was normal. His blood count, erythrocyte sedimentation rate, and the serum values for sodium, potassium, chloride, albumin, and globulin were normal. The benzodioxane test was negative. The urinary excretion of 17-ketosteroids was normal, with a mean value of 10 mg. in 24 hours. His heart was catheterized, and the resting pressure in the right atrium was 7 mm. Hg, in the right ventricle 80/10 mm. Hg, and in the pulmonary artery 34 mm. Hg (mean); the pulmonary capillary pressure was 28 mm. Hg. The pulmonary artery pressure rose to 64 mm. Hg (mean) after five minutes of exercise. The brachial artery pressure rose from 274/160 at rest to 314/186 during exercise. At rest the oxygen consumption was 179 ml. per minute per sq. m., with a cardiac output of 3·43 l. per minute per sq. m. Exercise for five minutes increased the oxygen consumption to 597 ml. per minute per sq. m., and produced a rise in cardiac output to only 5·17 l. per minute per sq. m. The blood-pressure was 240–200/170–130 on admission, and was unchanged after three weeks' rest in bed. Two weeks' treatment with oral hydrallazine, 300 mg. daily, produced a slight fall in blood-pressure to 230–150/160–110, but no symptomatic relief. An attempt was made to depress the blood-pressure by suppression of the adrenal cortex with cortisone. An oral dose of 75 gm. daily was given for seven weeks, but had no effect on the blood-pressure or the electrolyte balance. The mean daily excretion of urinary 17-ketosteroids increased to 15 mg. Both adrenal glands were removed on 22.11.54. They were normal in size and weight, and showed no abnormal histological features. Histological examination of sections of both kidneys, obtained by biopsy, showed the presence of severe arteriosclerosis with fibrinoid arteriolar changes. Towards the end of the operation there was a severe fall in blood-pressure, which persisted in spite of intravenous infusions of blood, saline, and noradrenaline. The pressure remained very low for eight hours, and the patient never regained consciousness and died 36 hours later.

Autopsy report (E. N. 379/54). The cause of death was widespread ischaemic cerebral softening; no thrombosis of a cerebral vessel was found. The heart was enlarged (680 gm.), and the left ventricle was grossly hypertrophied and dilated. The whole of the arterial tree showed severe atheromatous change, especially the cerebral arteries. Both kidneys were small, and additional histological sections confirmed the observations on the sections taken at biopsy. The pituitary and thyroid glands were normal, and no adrenal remnants were found.

Case 5. A married man aged 41 years, who had three children and worked as a grinder, was admitted to hospital on 22.12.54. He gave no family history of hypertension. For six months he had had headache, dyspnoea on exertion, orthopnoea, and paroxysmal nocturnal dyspnoea, and for two months his vision had been blurred. On admission his blood-pressure was 280–160/200–120, and his pulse was regular at 80 beats per minute. His heart was greatly enlarged, and there were fine râles at the bases of both lungs, but no venous distension or oedema of the legs. All peripheral pulses were palpable. A radiograph of the chest and an electrocardiogram showed great cardiac enlargement and left ventricular preponderance respectively. He had bilateral papilloedema, with retinal exudates and haemorrhages. His urine contained erythrocytes and granular casts, and 0·5 to 1·0 gm. of protein per 24 hours, and was sterile. He could concentrate urine to a specific gravity of only 1,014 after 12 hours without fluids. The blood-urea varied between 64 and 94 mg. per 100 ml., and the urine urea was more than 2 gm. per 100 ml. The creatinine clearance was 85 ml. per minute, and an intravenous pyelogram was normal. The blood count, erythrocyte sedimentation rate, and the serum values for sodium, potassium, chloride, albumin, globulin, calcium, phosphorus, and lipids were normal. The benzodioxane test was negative. The mean value of the urinary 17-ketosteroids was 10 mg. in 24 hours. His heart was catheterized, and the resting pressure in the right atrium was 5 mm. Hg, in the right ventricle 40/5 mm. Hg, and in the pulmonary artery 40/21 mm. Hg; the pulmonary capillary pressure was 12 mm. Hg. The pulmonary artery pressure rose from a mean value of 25 mm. Hg at rest to 59 mm. Hg after exercise for five minutes. The brachial artery pressure was 240/130 at rest, and rose to 296/144 during exercise. The consumption of oxygen was 149 ml. per minute per sq. m. at rest, and the cardiac output was 2·69 l. per minute per sq. m. After exercise the consumption of oxygen rose to 442 ml. per minute per sq. m., and the cardiac output was 4·98 l. per minute per sq. m. After four weeks' rest in hospital his blood-pressure was 250–190/160–130. Both adrenal glands were removed on 19.1.55. They were normal in size and weight, and showed no abnormal histological features. Histological examination of sections of the kidneys, obtained by biopsy, showed severe arteriosclerosis with fibrinoid arteriolar changes. The patient was given 100 mg. of cortisone by mouth on the day before operation, 200 mg. on the day of operation, 150 mg. daily in the subsequent two days, and 100 mg. daily in the following four days, a total of 1,000 mg. After the operation he improved at first, but his blood-pressure rose progressively to 260/180; on the sixth day after the operation he developed acute left ventricular failure, and died four hours later.

Autopsy report (E. N. 24/55). Death was caused by pulmonary oedema due to left ventricular failure. The heart weighed 715 gm., and the left ventricle was greatly hypertrophied and dilated, but no infarcts were seen. Severe atheromatous changes were present throughout the arterial tree, including the coronary arteries. Additional histological sections of the kidneys confirmed the observations on sections taken at biopsy. The pituitary and thyroid glands were normal, and no adrenal remnants were found.

Case 6. I. S., a housewife aged 37 years, without children, was admitted to hospital on 8.3.55. She gave no family history of hypertension. She had suffered for a year from increasingly severe headache, and had had two cerebrovascular accidents, 20 weeks and four weeks respectively before admission. Her blood-pressure was 250–210/170–130 on admission, and her pulse was regular at 80 beats per minute. Clinical examination showed no enlargement of the heart, but radiography and electrocardiography revealed left ventricular hypertrophy and preponderance respectively. She had no signs of congestive cardiac failure,

and all peripheral pulses were palpable. She had bilateral papilloedema; retinal haemorrheges and exudates were not present, but developed during the next two weeks. The urine contained a few erythrocytes and granular casts, and 0·2 to 0·4 gm. of protein per 24 hours, and was sterile. She was unable to concentrate urine to a specific gravity greater than 1,018 after deprivation of water for 12 hours. The blood-urea varied from 23 to 41 mg. per 100 ml., and an intravenous pyelogram was normal. The blood count, erythrocyte sedimentation rate, and the serum values for sodium, potassium, chloride, urea, albumin, globulin, calcium, phosphorus, and lipids were normal. The benzodioxane test was negative. The mean daily excretion of urinary 17-ketosteroids was 4 mg. in 24 hours. Her heart was catheterized, and the resting pressure in the right atrium was 5 mm. Hg, in the right ventricle 35/2 mm. Hg, and in the pulmonary artery 39/20 mm. Hg; the pulmonary capillary pressure was 10 mm. Hg. The pulmonary artery pressure rose from a mean value of 18 mm. Hg at rest to 30 mm. Hg after five minutes of exercise, and the pulmonary capillary pressure rose to 20 mm. Hg. The brachial artery pressure increased from 232/160 at rest to 240/180 on exercise. The cardiac output was 4·13 l. per minute per sq. m., with the consumption of oxygen 148 ml. per minute per sq. m., at rest. Exercise for five minutes increased the consumption to 312 ml. per minute per sq. m., and raised the cardiac output to 5·73 l. per minute per sq. m. After four weeks' rest in hospital the blood-pressure was 220–190/160–130, but the retinitis had greatly increased. The right adrenal gland was removed on 4.4.55, and the left on 25.4.55. Both glands were normal in size and weight, and showed no abnormal histological features. Histological examination of sections of the kidneys, obtained by biopsy, showed severe arteriosclerosis without fibrinoid arteriolar lesions. No cortisone was given for the first operation, and the blood-pressure returned to its previous levels by the seventh day afterwards. She was given 100 mg. of cortisone by mouth on the day before the second operation, 150 mg. on the day of operation and on the following day, 100 mg. and 75 mg. respectively on the next two days, then 50 mg. daily for three days, and 37·5 mg. daily for six days, followed by 50 mg. daily until she was discharged. On the fifth day after the second operation her blood-pressure returned to the level found before operation, but it then fell gradually to 160–130/120–80 by the sixth week, and the blood-urea rose gradually to the upper limit of normal. The serum-potassium level remained normal, but the serum-sodium decreased to the lower limit of normal. She was in positive nitrogen and potassium balance except for brief periods after each operation, but after the dosage of cortisone was reduced she was in negative sodium balance for a long time, and lost a total of 300 mEq. of sodium. Her weight decreased immediately after operation, but increased gradually thereafter. The urinary excretion of 17-ketosteroids averaged 7 mg. in 24 hours when the dosage of cortisone was 50 mg. daily, and consistently exceeded the values observed before operation. She was sent home on 11.6.55, feeling well, and without symptoms. Her weight (45 kg.) was unchanged, and she had no papilloedema, retinitis, or proteinuria.

Fourteen weeks after the operation her headache returned, and her blood-pressure was 200/130, but she had no papilloedema or proteinuria, and the serum electrolytes and urea were now normal. The dosage of cortisone was reduced from 50 to 37·5 mg. daily; her headache gradually disappeared, and her blood-pressure again fell gradually to normal. She has continued this dosage, and at present, 550 days after operation, she is well and without symptoms; although she asserts that her appetite is blunted, she has gained weight (to 51 kg.). She has no muscular weakness, but during the last six months there has been a moderate increase in the pigmentation of her skin. She is only slightly breath-

less on exercise, and the size of the heart and electrocardiogram are both normal. Her optic fundi are normal, and she has no proteinuria. Renal function has not deteriorated, and after deprivation of water she can now concentrate urine to a specific gravity of 1,022. Her menstrual cycle, which was normal before operation, was re-established seven weeks afterwards, and has been regular since. Her blood count, erythrocyte sedimentation rate, and the serum values for potassium, urea, calcium, phosphorus, alkaline phosphatase, albumin, globulin, and lipids are normal, but the serum-sodium is consistently at the lower limit of normal.

Summary

1. Bilateral adrenalectomy was performed on six patients with severe essential hypertension.

2. Two patients died shortly after, and a third seven weeks after operation.

3. Three others have lived from 19 to 30 months after operation, are free of all symptoms, and have normal blood-pressure. They show a reduction in the size of the heart, remission of the retinal changes, and no reduction of renal function.

4. Detailed biochemical balance studies are reported.

5. The mechanisms responsible for the fall in blood-pressure after adrenalectomy are discussed.

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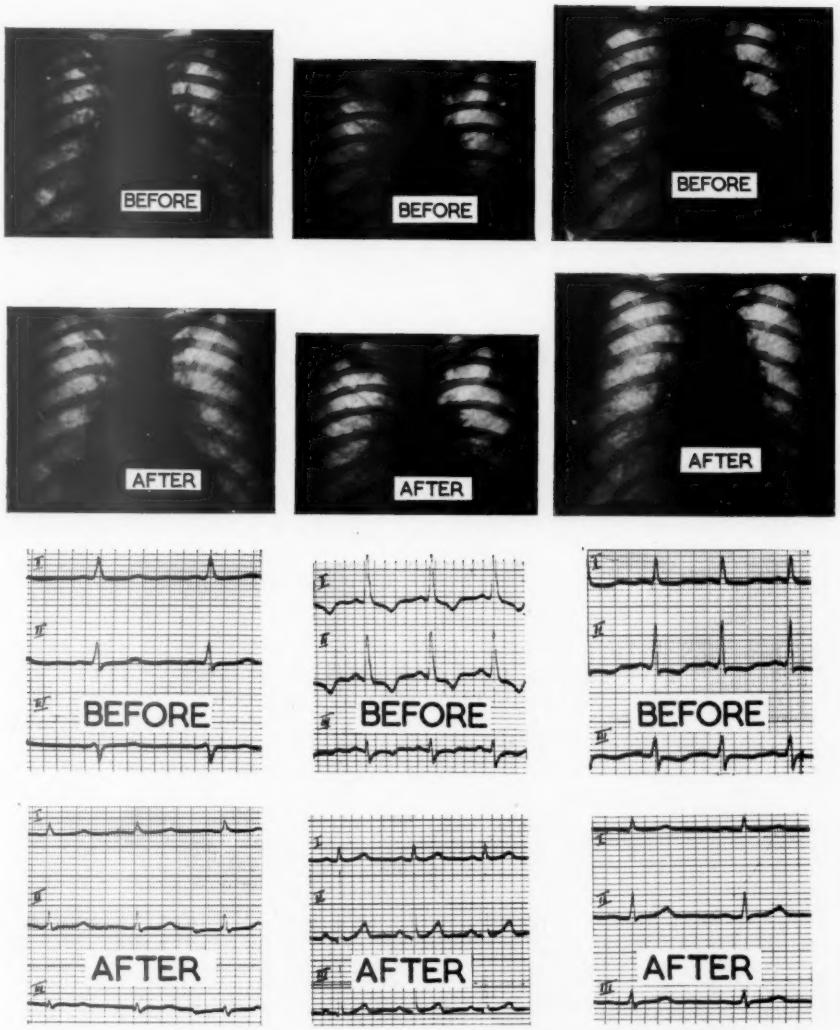

Case 2 Case 3 Case 6

FIG. 8. Postero-anterior radiographs and electrocardiograms of Cases 2, 3, and 6, taken before and 900, 750, and 550 days respectively after adrenalectomy

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A CLINICAL AND BIOCHEMICAL STUDY OF HEPATO-LENTICULAR DEGENERATION (WILSON'S DISEASE)[1]

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With Plate 46

The interrelation of liver cirrhosis with degeneration of the basal ganglia of the brain in Wilson's disease has attracted considerable interest, and some light is thrown on the pathogenesis of this association by a careful study of copper and aminoacid metabolism. This subject has become the focus of recent research, and numerous reviews and contributions have been published within the last four years (Matthews, Milne, and Bell, 1952; Brick, 1952; Uzman and Hood, 1952; Uzman, 1953; Bearn and Kunkel, 1952; Spillane, Keyser, and Parker, 1952; Scheinberg and Gitlin, 1952; Bickel, 1952; Denny-Brown, 1953; Palmer, Drew, and Chenoweth, 1953; Franklin and Bauman, 1953; Bearn, 1953; Bearn and Kunkel, 1954 *a*, *b*; Stein, Bearn, and Moore, 1954; Zimdahl, Hyman, and Stafford, 1954; Earl, Moulton, and Selverstone, 1954; Blaha, Gastager, Tschabitscher, and Wewalka, 1954; Hornbostel, 1954; Warnock and Neill, 1954; Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe, and Bean, 1954; Tyler and Armstrong, 1954; Schreier, 1955; Bearn and Kunkel, 1955; Scheinberg, Dubin, and Harris, 1955; Markowitz, Gubler, Mahoney, Cartwright, and Wintrobe, 1955; Bush, Mahoney, Markowitz, Gubler, Cartwright, and Wintrobe, 1955; Bickel and Souchon, 1955; Bickel, 1955). The most important facts emerging from these studies, and from our own observations, may be summarized as follows. Disturbance of copper metabolism is an essential feature of Wilson's disease, and is manifested by cupruria, decreased copper output in the stools, copper accumulation in various organs, a low total copper content in the serum or blood, and a deficiency of the enzyme coeruloplasmin, an α-globulin which normally accounts for at least 90 per cent. of the serum copper (Holmberg and Laurell, 1947, 1948), but the function of which in the body is at present obscure. Aminoaciduria is generalized in that some 10 or more aminoacids are excreted in excess in the urine, and its mechanism seems to be mainly renal, though some prerenal factors are probably also involved (see page 552); in contrast to the cupruria, however, aminoaciduria is a feature of most, but not all, patients with Wilson's disease. Furthermore, Uzman and Hood (1952) claimed that besides aminoaciduria there is peptiduria, which they considered to be the primary abnormality, while glycosuria and proteinuria have also

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repeatedly been observed; the relationship between these findings, and their pathogenic importance, are still far from clear. Apart from metabolic studies, much time has been devoted to therapeutic attempts. The only promising approach so far has been the attempt to remove some of the excess of copper from the liver and brain by the use of BAL (2:3 dimercaptopropanol), and more recently of EDTA (ethylenediamine-tetra-acetic acid, 'versene'), a new agent which forms complex salts with various metallic ions and removes them from the body.

During the past five years we have had the opportunity of studying the clinical features and the copper and aminoacid metabolism of 12 patients with Wilson's disease from eight families; five further siblings of our patients probably succumbed to the disorder, though clinical, and especially biochemical, data are incomplete. Our work was mainly concerned with the investigation of the copper content of the urine, serum, and various organs, with copper balance studies, with the total and individual aminoacid content of blood and urine, and with the influence of the copper-removing agents BAL, molybdenum, and EDTA ('versene') upon copper and aminoacid metabolism.

Clinical Observations

Some clinical and biochemical details are given in Table I. Among the 12 proven cases there were four pairs of siblings (Cases 2 and 8, 3 and 7, 4 and 11, 6 and 10); five further siblings (Cases 13 to 17) had probably died of the same disease. None of the patients' parents, or members of the family other than siblings, were clinically affected; this is in agreement with the observations of Lüthy (1931), Dent and Harris (1951–2), Matthews, Milne, and Bell (1952), and Bearn (1953), and suggests a recessive mode of inheritance; consanguinity of marriage existed only in the family of Case 5. In six of the eight families tests for aminoacid and copper excretion were carried out in the urine of all the parents and nearly all the live siblings; by this means Cases 2, 3, and 10 were detected. Recently another brother of patients 6 and 10 was found to have a reduced serum-copper level of 72 μg. per 100 ml., though up to then he had shown no clinical or other biochemical abnormality. None of the other siblings or parents of our patients showed increased amounts of copper or aminoacids in their urine, but the father of patients 6 and 10 had a serum-copper level of 84 μg. per 100 ml., and both parents of patients 2 and 8 had low levels—the father 45 μg. and the mother 71 μg. per 100 ml.

At the appearance of the first symptoms eight of the 12 patients were 11 years old or younger; the youngest was seven, the eldest 35 years of age. The two youngest patients (Cases 2 and 3) were free from marked symptoms for two years after the diagnosis had been made. In addition to liver enlargement, both showed cupruria and low serum-copper levels; these biochemical findings were present in all our patients and, with coeruloplasmin deficiency, we believe them to be the earliest and diagnostically most important evidence of the disease. All patients showed the characteristic greenish-brown or greenish-yellow corneal

discoloration (Kayser-Fleischer ring), though in the two youngest children it was so faint at first as to be indistinguishable to the naked eye, and was only just apparent under the slit-lamp. In a 12-year old boy (Case 6), on the other hand, the ring was very conspicuous and most useful in establishing the diagnosis, as, apart from repeated attacks of violent behaviour, he was free from symptoms, and the liver was impalpable, though the biochemical changes were characteristic.

We were impressed by the great variability of clinical symptoms (Table I). In five of the 12 patients the disease started with localized tremor or involuntary movements, and three others showed evidence of mental deterioration and emotional instability. In two patients there had been a history of short attacks of jaundice, while three others complained of pain in the upper abdomen and an aversion to fat, or temporarily passed dark urine and light-coloured stools. Oedema or ascites was reported in three of our 12 patients and in two of the incompletely studied siblings, and two patients of each group had had attacks of acute or subacute nephritis (Cases 5, 6, 14, and 15). Marked signs of renal damage have rarely been recorded in Wilson's disease, and no pathological changes in the kidneys were seen at autopsy in three of our patients (Cases 7, 9, and 12). Discrete evidence of some kidney disturbance is, however, not so rare: apart from early proteinuria and haematuria, mild proteinuria was repeatedly observed in three further patients (Cases 2, 7, and 11); aminoaciduria, glycosuria, and increased loss of uric acid in the urine (Mahoney, Sandberg, Gubler, Cartwright, and Wintrobe, 1955) are also further evidence. Urea clearance and concentration tests and water dilution and concentration tests were carried out only in Cases 1, 4, 9, and 10, and gave normal results; centrifuged urine deposits were generally normal; blood-urea estimations were repeatedly normal.

The fully developed clinical picture presented many well-recognized symptoms (for details see Table I), but at times more bizarre forms were encountered. One patient (Case 5) was psychotic, with schizoid and paranoid ideas and olfactory and auditory hallucinations (a similar case was described by Herz and Drew, 1950); in Case 7 there was early mental decay with violence, especially severe at times, and the latter feature was also prominent in Case 6, while another patient (Case 8) showed peculiar periodic attacks of drowsiness. In Case 12, on the other hand, apart from tremor, there was little or no neurological or mental abnormality, but the patient suffered from portal hypertension, and died in liver coma. Another patient (Case 13), in whom the diagnosis seems probable, also died from liver necrosis within a year of the onset of symptoms, and before mental or neurological changes developed. It was, however, more usual to see the early exhibition of liver symptoms recede while neurological and mental deterioration progressed (Cases 1, 4, 5, and 6). But, in spite of the severe liver destruction seen at autopsy or in liver biopsy (Case 6), hepatic symptoms were generally inconspicuous, and only three of the 12 patients (Cases 6, 11, and 12), at the height of their illness, had major complaints which were hepatic in origin. Liver-function tests gave only slightly abnormal results

TABLE I. *Summary of Clinical Features of 12 Cases of*

Case number	*Initials and sex*	*Age at onset (years)*	*First symptoms*	*Age at first admission (years)*	*Main features*
1	R. S. M	7	Febrile jaundice, hepatomegaly, swelling of calves and thighs	11 11/12	Vacant facies, fatuous smile, dysarthria, tremor, unsteady gait, rigidity, emotional instability
2	B. H. F	7	Frequent stumbling, intellectual deterioration, poor appetite	7 8/12	Emotional instability, skin pigmentation, spider naevi; otherwise healthy appearance
3	P. V. F	7	Looked pale and yellowish; seemed quieter than usual, but otherwise healthy	..	..
4	E. W. M	9	Involuntary movements; 3 yrs. later abdominal episode, fever, hepato-splenomegaly	12 8/12	Vacant facies, stereotyped smile, dysarthria, involuntary movements, action tremor, extrapyramidal gait, rigidity, childishness
5	R. K. M	9	? Pneumonia, acute glomerulonephritis; since then repeated attacks of fever and epigastric pain; intolerance of fat. 3 yrs. later hepato-splenomegaly	25 (Outpatient only)	Extrapyramidal features, uncoordinated walking; action tremor, some dysarthria, schizoid psychosis, hallucinations, mental decline
6	R. N. M	9	Oedema of legs, ascites, abdominal pain; dark urine, pale stool, fever, proteinuria, haematuria; blood-pressure 140/120. Tremor of tongue	12 11/12	Slight tongue tremor, otherwise no neurological or mental symptoms except attacks of bad temper and violence. Healthy appearance
7	J. V. F	10	Started to wander off alone, to speak indistinctly, and to deteriorate intellectually	12 8/12	Extrapyramidal facies and posture, rigidity. Mentally backward, emotionally very unstable, incontinent, noisy, and aggressive
8	A. H. F	11	At 7 yrs. slight attack of jaundice. At 11 first attack of drowsiness, apathetic, incontinent, 'wild-eyed', loss of appetite, slurred speech; did not recognize mother	14 11/12	Vacant facies, constant grin, euphoria, dysarthria, tremor, involuntary movements, unsteady gait, rigidity in legs
9	J. B. F	15	School work deteriorated; 1 yr. later developed tremor of limbs, nasal speech	16	Emotionally very labile, flapping action tremor, muscle rigidity, spider naevi
10	E. N. M	14	Kayser-Fleischer ring observed during family investigation. At 18 yrs. action tremor left arm	19	Gross action tremor spreading over whole body; dysarthria, uncoordinated gait, muscle rigidity; intelligent but rather euphoric and childish; fatuous smile
11	J. W. M	14	Pain in dorso-lumbar region, difficulty in walking. At 20 yrs. tremor, rigidity, and vacant facies	25	Mentally dull; extrapyramidal facies and posture; unable to stand. Coarse tremor, rigidity, distended abdominal veins, skin pigmentation, purpuric rash, ankle oedema
12	S. M. F	35	Shaking of right hand, 2 yrs. later of head and left hand. No abdominal symptoms	37	Pale, thin, tired; action tremor of hands, head, neck. No other neurological or mental symptoms
Incomplete case records of affected siblings:					
13	G. S. M	8	Anaemic; loss of appetite; less active	..	..
14	D. W. F	10	Subacute nephritis with oedema, haematuria	..	..
15	S. N. F	12	Diarrhoea, oedema and ascites, proteinuria, haematuria	..	..
16	S. B. F	12	Headache, slurring speech, nose bleeding, dribbling	..	..
17	B. B. M	15	Dragging and unsteadiness of right leg, weakness of right arm, dysarthria	..	..

Wilson's Disease, with notes on Five Affected Siblings

Case number	Kayser-Fleischer ring	Hepatomegaly	Splenomegaly	Cu level in blood	Cu in urine	Aminoaciduria	Glycosuria	Liver function tests	Treatment and course of disease	Age at 1.1.54 or at death ✠ (years)
1	+	−	±	Low	+	+	−	±	9 BAL courses; molybdenum; EDTA by mouth; copper-restricted diet. Slow progression; recently convulsions, coma	14 $\frac{1}{12}$
2	±	+	−	Low	+	−	±	−	10 BAL courses; EDTA by mouth; copper-restricted diet. Kayser-Fleischer ring and skin pigmentation increased. Liver smaller (? atrophy), spleen larger; some liver-function tests abnormal. Walking deteriorated. Marked aminoaciduria. Rapid final decline; death in coma following hyperpyrexia	10 $\frac{11}{12}$ ✠
3	±	+	−	Low	+	−	±	..	..	7
4	+	+	±	Low	+	+	−	−	1 BAL course; molybdenum; EDTA by mouth. Progressive neurological with subsequent mental deterioration. Skin pigmentation appeared; liver reduced, spleen larger; liver-function tests mainly normal	14 $\frac{3}{12}$ ✠
5	+	−	−	Low	+	+	+	±	4 BAL courses; EDTA by mouth; copper-restricted diet. At first rapid deterioration, now perhaps some improvement of psychosis. No change in neurological symptoms	25 $\frac{1}{2}$ (1.8.54)
6	+	+	+	Low	+	+	−	±	Molybdenum; EDTA by mouth and injection. Slow mental deterioration; abdominal crisis. Some liver-function tests abnormal. Sudden death in coma with generalized rigidity after haematemesis	15 $\frac{8}{12}$ ✠
7	+	−	±	Low	+	+	+	−	1 BAL course, but patient became quite unmanageable. Transfer to mental hospital; molybdenum therapy. Transient improvement, then rapid mental decay and neurological deterioration. Died in coma	13 $\frac{5}{12}$ ✠
8	+	±	±	Low	+	+	−	±	At beginning of 1st BAL course she fell into a comatose state (see column 4) in which she died 6 weeks later	15 $\frac{8}{12}$ ✠
9	+	−	−	Low	+	+	−	−	Despite 5 BAL courses, progressive mental and neurological deterioration; died in state of decerebrate rigidity and hyperpyrexia	18 ✠
10	+	−	−	Low	+	+	±	−	EDTA by mouth and injection. So far no further progression of disease. BAL therapy abandoned after 4th injection because of toxic reaction	19 $\frac{4}{12}$
11	+	−	+	Low	+	+	+	±	No treatment. Increasing oedema, further mental decay; died at home soon after discharge	25 ✠
12	+	−	+	Low	+	+	−	+	Gradual deterioration with massive ascites, oedema of legs, marasmus; death in liver coma. Few neurological, no mental symptoms	40 ✠
13	..	..	..	..	..	..	..	..	Jaundice 1 month before death; died of liver necrosis. No neurological or mental symptoms	9 ✠
14	..	..	+	..	..	..	..	..	Oedema receded, but mental deficiency with violence, action tremor, haemorrhagic diathesis, splenomegaly, and deep ulcers of skin developed	16 ✠
15	+	..	+	..	..	..	..	+	Ascites receded; at 13 yrs. extrapyramidal facies and gait, emotional instability, dysarthria, tremor, contractions. Babinski reflex on left. Before death epistaxes, jaundice, rigidity, thirst, polyuria	14 $\frac{1}{2}$ ✠
16	..	..	..	..	..	..	..	..	Became very bad-tempered, negative, violent; developed spastic gait, aggressiveness, and mental decay. Transferred to mental hospital, where she died	17 ✠
17	+	..	..	..	..	..	..	..	Parkinson-like facies and tremor of limbs, rigidity. Mental and neurological deterioration; death after fall from window (? suicide)	20 ✠

in all patients save one (Case 12), though indication of liver disturbance can be found at some time in most patients (see also Franklin and Bauman, 1953). But at one time or another nearly all our patients showed some such symptoms as enlargement of the liver or spleen, ascites or oedema, jaundice, abdominal crises (one of our patients—Case 6—had an urgent laparotomy performed because an acute abdominal condition was suspected, but only advanced liver cirrhosis was found at operation), haematemesis as a result of bleeding from oesophageal varices, or cutaneous changes such as the development of diffuse light-brown pigmentation, especially over the front of the abdomen, or of spider naevi on trunk or limbs. In Case 7 the last liver-function tests, five weeks before death, gave normal results, in spite of the advanced cirrhosis and atrophy found at autopsy. Active regenerative processes during chronic liver destruction over many years may partly explain this discrepancy, and such islets of regenerated liver parenchyma may even furnish normal needle biopsy material, despite the presence of advanced cirrhosis and liver atrophy (Case A. G. of Denny-Brown, 1953). The final stages of the disease were observed in Cases 2, 7, 9, and 12. In Case 12 death was due to liver insufficiency, but in Cases 2, 7, and 9 the clinical picture was that of neurological and mental disorder, the patients becoming bed-ridden and slowly progressing to a state of decerebrate rigidity, though in Cases 7 and 9 the patients still retained consciousness, and responded to questions or commands, shortly before death.

Biochemical Observations

Methods

Estimation of copper. All analyses were carried out in duplicate, except in the few instances in which the specimen was sufficient only for a single determination. The method (F. C. Neale, to be published) involved wet ashing, and was based on that of Eden and Green (1940). It cannot be over-emphasized that the avoidance of contamination by traces of copper demands perfect cleanliness of glassware and purity of reagents, and especially an ample supply of copper-free glass-distilled water. Reagents used were AnalaR throughout except for ammonium citrate, which is available only in B.P. quality and contains copper contamination in amounts ranging from 0·8 to 4·5 parts per million. Ammonium citrate is therefore best prepared from AnalaR citric acid and ammonia and further purified by the use of sodium diethyldithiocarbamate and amyl alcohol.

For *serum estimations* 25 ml. of blood were taken directly into clean copper-free centrifuge tubes through a dry sterilized needle made from stainless steel tubing. Five-ml. portions of serum in special micro-Kjeldahl flasks, graduated at 40 ml. on the stem and carrying a ground-glass joint, were treated in turn with sulphuric acid (2 ml.) and nitric acid until ashed, and then, after dilution, with 50 per cent. ammonium citrate (2 ml.), concentrated ammonia solution (10 ml.), and 1 per cent. sodium diethyldithiocarbamate (0·25 ml.), and made up to the graduation mark. The yellow copper diethyldithiocarbamate was extracted into amyl alcohol (5 ml.) and its extinction coefficient at 435 mμ

measured in a Unicam quartz spectrophotometer. A calibration curve was derived from standards containing 2 to 30 μg. of copper carried through the same procedure.

For *urine estimations* specimens were collected in vessels thoroughly cleaned with chromic acid and rinsed with glass-distilled water. Of patients' urine 10 ml. portions (of normal urine 50 ml.) were taken and treated as described for serum.

For *faecal estimations* stools were collected directly in acid-washed glass jars, a convenient volume of hot strong sulphuric acid was added, and the homogenized specimen diluted with glass-distilled water to a final concentration of 40 per cent. H_2SO_4; 5 ml. portions were taken, nitric acid was added, and the estimation carried out as above.

For *food estimations* 24 hours' replicate meals were treated in Pyrex glass vessels with hot strong sulphuric acid, and the copper estimated as above.

Autopsy material. Minimal handling with instruments made of stainless steel was aimed at. The specimens were dried in a glass dish at 110° C. to constant weight, 2 gm. samples were wet-ashed, and measured portions used for the estimation of copper content.

Estimation of aminoacids. Paper chromatography, microbiological assay, formol titration, and the gasometric ninhydrin method were used to determine the individual and total aminoacid content of urine and plasma. Paper chromatography was two-dimensional, with phenol-water as the first and collidine-lutidine-water as the second solvent. The urine specimens were either fresh fasting samples or 24-hour collections preserved with chloroform and glacial acetic acid. The urine volume used for each chromatogram corresponded to 500 μg. of non-protein nitrogen. After their development with ninhydrin, the colour and size of the aminoacid spots were compared with test spots of 5, 10, 20, 40, and 60 μg. of pure taurine, which were run on the same paper (Bickel and Souchon, 1955). Microbiological assay was carried out according to the technique of Schreier and Plückthun (1950, 1949–50), which is essentially that of Henderson and Snell (1948). *Leuconostoc mesenteroides* P-60 was used for the assay of tyrosine and valine, *Lactobacillus arabinosus* 17–5 for tryptophan and phenylalanine, and *Streptococcus faecalis* for arginine. The pH of the incubated final medium was measured by a Cambridge glass-electrode pH-meter. The plasma was heparinized, and was deproteinized by Folin's method with 0·66N H_2SO_4 and 10 per cent. sodium tungstate. Each sample was assayed in at least two, and generally three, different solutions, and two standard curves were prepared for the assay of each aminoacid. For the estimation of the total α-amino nitrogen in plasma and urine, the gasometric ninhydrin method was carried out as described by Hamilton and Van Slyke (1943) and Van Slyke, MacFadyen, and Hamilton (1943). Though this is the most specific procedure, the formol-titration method of Folin (1922) is less laborious, and was applied to the study of the aminoacid excretion under the influence of various copper-removing agents.

Other methods. Sugar excretion was tested by one-dimensional paper chromatography. The solvent was a mixture of butanol, ethanol, water, and ammonia;

the developer was aniline phthalate in butanol (Bickel and Souchon, 1955). Molybdenum was estimated by the method of Marmoy (1939). Other methods used were those commonly employed in a biochemical laboratory.

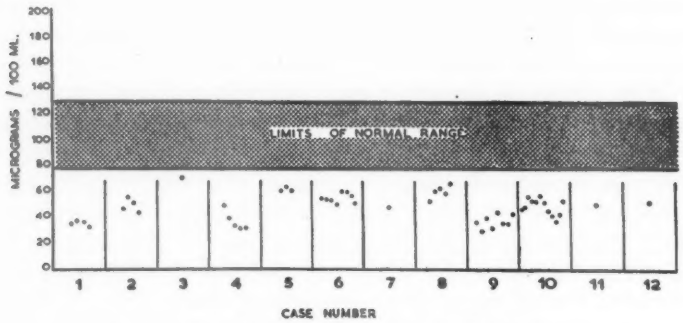


FIG. 1. Serum total copper levels in Wilson's disease.

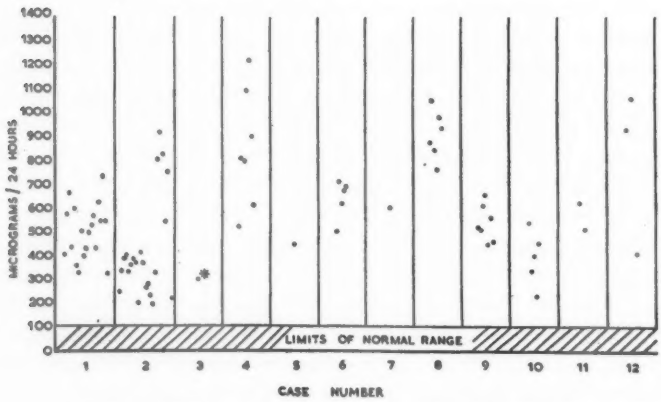


FIG. 2. Daily urinary copper excretion in Wilson's disease.

*A single specimen only of urine was available in Case 3, containing 37 μg. of copper per 100 ml. The daily output was calculated on the assumption of a mean normal volume of urine for a seven-year-old child.

Details of administration of BAL, molybdenum, and EDTA ('versene')

BAL was given by deep intramuscular injection, as a 5 per cent. solution in arachis oil containing 10 per cent. benzyl benzoate. The dosage was usually 2 mg. per kg. body-weight for each injection, and each course of BAL consisted of two or three injections daily for 10 to 12 days, except in Case 5, in which one injection was given daily for 20 days.

Molybdenum was administered by mouth as ammonium molybdate, in daily amounts of from 5 to 20 mg. of molybdenum per kg. body-weight. In Cases 4 and 7 supplements of sulphate, as 5 gm. sodium sulphate daily, were given

temporarily, as Dick (1953) suggested that inorganic sulphate was required to enable molybdenum to exert a limiting effect on copper storage.

EDTA ('versene') has been administered exclusively as the disodium calcium salt, for reasons of solubility, and to avoid reducing the serum-calcium level. Oral doses of 30 mg. per kg. body-weight a day were given, and were in some cases increased to a maximum of 75 mg. per kg. a day without any adverse effect (one tablet of 'versene' = 0·25 gm.). Intravenous administration consisted of a test dose of 0·2 gm. of EDTA, followed after 12 hours by the full dose of 1 gm., which was given twice daily as a slow infusion, lasting 60 minutes, in 200 ml. of isotonic saline or glucose. As this method is rather inconvenient, we later gave two intramuscular injections daily of 5 ml. of a 20 per cent. EDTA solution, mixed in the syringe with 0·5 ml. of 2 per cent. procaine hydrochloride (= 2 gm. EDTA daily), up to a maximum of 10 days. This had the same effect on copper metabolism as intravenous EDTA. No untoward reactions, and particularly no significant drop of the serum-calcium level, were observed after either period of administration, and oral dosage with EDTA during many months did not produce any skeletal changes visible by X-ray examination.

Results

Serum-copper levels. Some total copper levels in the serum of the 12 patients are shown in Fig. 1; these values were mostly obtained from early morning fasting specimens. In all patients the copper levels were reduced, generally to one-half or one-third of the average normal value of 100 to 120 μg. per 100 ml. Some relation of the serum-copper level to the severity of the disease is suggested by the fact that the youngest and earliest patient (Case 3) showed only a slightly reduced copper level before the onset of clinical signs, whereas in the advanced Cases 1, 4, and 9 there was a considerable and constant reduction. In the absence of drugs the levels were found to be remarkably constant over long periods of time.

Urinary copper excretion. All patients had marked cupruria. Some values obtained when the patients were not undergoing treatment are given in Fig. 2, and show a copper excretion ranging from about 250 μg. to over 1,000 μg., compared with the normal range of 0 to 100 μg., in 24 hours. Again, some correlation between cupruria and severity of the disease is suggested by low values of under 200 μg. in 24 hours at the beginning of the disease in Case 2, and of 37 μg. per 100 ml. in a single urine specimen from a patient still free from symptoms (Case 3). The highest copper excretion was found in advanced cases, such as Cases 4, 8, and 12, but in the final stages of the disease complete 24-hour urine collections became difficult, and the values for such patients (Cases 7, 9, and 11) must be regarded with some reserve. In spite of individual variations, however, cupruria, like hypocupraemia, must be regarded as an early biochemical abnormality of the disease; our observations did not enable us to determine which appeared first. In individual patients the daily copper excretion varied rather more than the serum-copper level. On a constant intake of dietary copper the variations were much reduced, and the urine volume had a

direct bearing on the daily copper output. During radioactive copper studies (unpublished data), in which copper estimations were carried out in many different portions of the 24-hour output, the overnight specimen usually contained the highest copper concentration, and this gradually decreased during the morning, rising steadily again during the afternoon. The late evening specimens frequently showed concentrations as high as the overnight specimens, and occasionally higher.

TABLE II

Copper Content in Organs of Patients with Wilson's Disease and of a Woman who Died from Pneumonia with Heart Failure

(Expressed as mg. copper per 100 gm. of dried organ)

	Case 2		*Case 9*		*Control subject**	
Organs	*No. of estimations*	*Average*	*No. of estimations*	*Average*	*No. of estimations*	*Average*
Liver	1	57·7	4	29·0	2	4·4
Cornea	..	..	1	28·4	..	..
Brain:						
Caudate nucleus	1	30·8	1	30·7	2	3·0
Putamen	1	18·7	1	19·4	..	..
Putamen and globus pallidus	1	20·8	..	..	..	..
Frontal lobe	..	..	2	18·3	2	2·0
Cerebellum	..	..	2	17·8	2	2·4
Parietal lobe+stem	..	..	2	16·4	..	..
Globus pallidus	..	..	1	5·6	2	2·7
Kidneys	1	24·2	3	9·0	2	1·4
Dorsal cord with dura	..	..	2	4·6	2	0·9
Iris and lens	..	..	1	3·6	..	..
Rest of eye	..	..	1	2·8	..	..
Left heart ventricle	..	..	2	1·7	2	2·2
Lungs	..	..	2	1·7	2	1·7
Jejunum	..	..	3	1·0	2	1·8
Stomach	..	..	2	1·0	2	1·2
Spleen	1	0·52	2	0·9	2	1·5
Pancreas	1	1·35	..	..	..	..
Colon	..	..	3	0·8	2	1·3
Suprarenals	..	..	2	0·8	2	0·7
Muscles from leg	..	..	2	0·5	2	0·6
Skin from leg	..	..	2	0·3	2	0·8
Bile (mg./100 ml.)	..	0·264	2	0·12	..	1·0† 1·1 1·0
Cerebrospinal fluid (mg./100 ml.)	1	0·637	..	..	..	..

* The organs, especially the lungs, contained more blood than those of cases 2 and 9.
† Single estimations on bile of three subjects collected at autopsy.

Copper content of the organs. The copper contents of various organs obtained from Cases 2 and 9 were estimated and compared with those of a patient who died of pneumonia with heart failure (Table II). An increase of copper was found, particularly in the liver, various parts of the brain, the kidneys, and the dorsal cord; the concentration in the cornea was also high, though for this tissue no control values were available. In Case 9 the caudate nucleus contained most and the globus pallidus least copper, and in Case 2 both putamen and globus pallidus had similar copper concentrations, but here also less than the

caudate nucleus. The copper contents of the other organs were comparable with those of the control organs. The low copper concentration of the bile, which was taken from the gall-bladder, was probably not a significant finding, as at autopsy in Case 7 the gall-bladder bile was found to contain 1·11 mg. per 100 ml., which is close to the values found in the three control specimens; subsequently three further control specimens of bile gave values ranging from 0·07 to 0·69 mg.

TABLE III

Copper Balances in Three Patients and in a Normal Control

(Three-day mean values, in mg. per day)

	Control, aged 10 yrs.	*E. W., aged 13 yrs.*	*B. H., aged 8 yrs.*	*R. N.*	
				aged 12 yrs.	*aged 13 yrs.*
Intake:	1·42	1·57	1·26	1·58	1·71
Output:					
Urine	0·08	0·60	0·45	0·58	0·60
Faeces	1·39	0·89	0·74	1·08	1·18
Total	1·47	1·49	1·19	1·66	1·78
'Absorption'	0·03	0·68	0·52	0·50	0·53
Retention	−0·05	+0·08	+0·07	−0·08	−0·07

per 100 ml. It must finally be stressed that the copper levels in the organs in Cases 2 and 9 cannot be regarded as characteristic of the disease, as in Case 2 the patient received monthly courses of BAL, with continuous oral EDTA between the courses, for nearly two years, and the other patient (Case 9) had been given five courses of BAL during the 18 months before death. Palmer, Drew, and Chenoweth (1953) showed that BAL treatment considerably reduced the copper content of the brain and liver of their patient. In our patients it is noteworthy that the splenic copper concentration in each case was similar to that of the control. This may suggest that the body's more easily accessible copper—estimated at 25 to 40 mg. by isotope dilution studies (A. Quinton, F. C. Neale, and H. Bickel, unpublished observations)—is in this organ. In Cases 2 and 7 the post-mortem copper levels in the cerebrospinal fluid were found to be 637 μg. and 146 μg. per 100 ml. respectively, in strong contrast to a level of 10 μg. per 100 ml. found in Case 10 during life.

Copper-balance studies were carried out in three patients (Cases 2, 4, and 6), and in a healthy boy of 10 years awaiting operation for inguinal hernia. The diet was a mixed one, but was kept constant for a week before and during the experiment. The beginning and end of a three-day stool collection was marked by oral carmine; all urine passed during this time was collected, and replicate meals also were reserved for analysis. Such short balance experiments may not properly reflect the continuous, if variable, copper retention over a period of years, which in this disease must clearly be present to account for the final accumulation of the metal in the organs. It does not, however, seem necessary to suppose more than a very slightly positive balance to produce, during the course of say 10 to 20 years, the additional amounts of deposited copper which are found. Our results (Table III) do in fact indicate, within the limits of experimental error, a complete balance. The retention of approximately 43 to

72 per cent. of the daily copper intake, reported by Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe, and Bean (1954), if continued indefinitely, should lead to higher autopsy values than have yet been observed. It may therefore be that the rate of copper accumulation is markedly variable in a given subject, and that the clinically fluctuating course of the disease, so well described by Barnes and Hurst (1925), is also reflected biochemically. These balance studies clearly demonstrate the greatly increased copper output in the urine, and the diminished output in the stool, compared with the control.

TABLE IV

Effect of BAL on Copper Excretion in Five Patients

(μg. copper in 24 hours)

	Case 1					Case 2					
	I	II	III	IV	V	I	II	III	*Case 4*	*Case 8*	*Case 7 (μg./100ml.)*
Before BAL	569	..	..	..	..	..	..	..	..	867	
	657	..	..	..	519	394	..	..	..	832	
	427	350	495	422	561	324	..	275	793	755	
	595	319	390	488	423	353	197	223	785	974	103
During BAL	924	737	1,132	800	618	771	444	423	1,231	1,265	222
	911	694	629	824	824	595	763	337	1,277	..	182
	986	724	684	918	723	676	516	310	756	1,000	169
	680	832	660	751	613	446	355	189	583	1,825	238
	1,064	597	657	577	766	807	347	391	670	..	175
	819	618	643	751	793	752	388	281	532	..	103
	758	627	744	643	726	542	465	199	546	..	142
	677	409	606	655	568	462	480	326	..	..	
	955	528	..	775	697	330	378	328	..	..	
	878	483	460	782	480	496	449	349	..	..	
	532	472	492	638	506	379	365	247	..	..	
After BAL	436	401	303	711	371	363	404	244	..	1,224	
	249	169	210	398	336	..	372	193	..	1,241	
	402	396	235	457	230	..	258	130	..	757	
	577	360									

The influence of copper-removing agents on copper metabolism

Attempts to mobilize and remove some of the copper accumulated in the body in this disease were undertaken with three different agents:

1. *BAL.* The mode of action of this drug and its practical application in Wilson's disease are well established (Denny-Brown, 1953; Hornbostel, 1954). BAL was given to eight of our patients (Cases 1, 2, 4, 5, 7, 8, 9, and 10), but in Cases 4, 7, 8, and 10 the treatment was discontinued after a few injections for various reasons, such as the occurrence of toxic symptoms, the very advanced stage of the disease, substitution of other forms of therapy, or transfer of the patient to a mental hospital. Of the toxic reactions to BAL, those encountered in Case 8 were the most sudden and severe: on the third day, after the seventh injection, the girl became drowsy, suffered from nausea, and lapsed into coma, in which she died six weeks later. No adequate cause for the coma was found; no serum-copper estimations were performed, but urinary copper excretion had risen to 1,825 μg. in 24 hours (Table IV).

Patients 1 and 2 were treated the longest, the latter receiving 10 courses of BAL injections within 16 months, and the former nine courses within 17 months. In Case 2 treatment was started very early, at a practically symptom-free stage

of the disease, while the girl was still attending school. The cupruria, which was still mild, doubled during the first few days of BAL therapy (Table IV), but in spite of prolonged treatment with BAL the Kayser-Fleischer ring and skin pigmentation increased, severe aminoaciduria developed, and subsequent

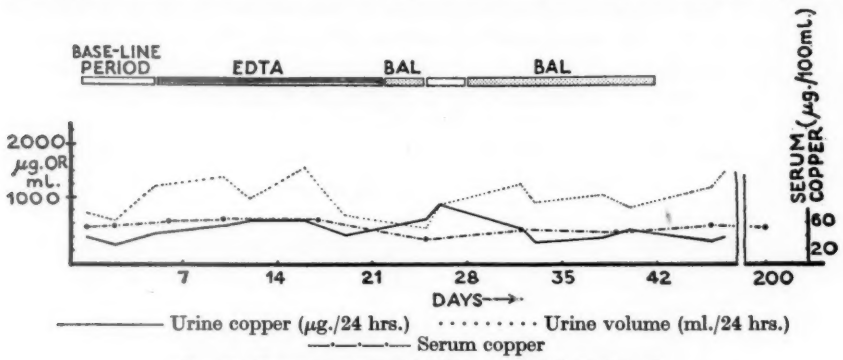


FIG. 3. Response to oral EDTA and BAL in Case 5.

treatment with EDTA did not prevent her death. Patient No. 1, who at the beginning of BAL therapy had the disease in a definite but not advanced form, and whose illness had shown some fluctuations previously, appeared unchanged after five courses, the Kayser-Fleischer ring remaining unaltered in size and colour. But later, despite the combination of BAL with molybdenum or EDTA therapy, the patient showed definite mental and neurological deterioration. As in other cases, copper excretion in the urine increased during BAL treatment, but only temporarily (Table IV); after about a week the starting level was usually reached, and thereafter the excretion often fell for a few days to below the usual values for these patients. In Case 9 there was likewise no permanent improvement, but after the third and fourth courses a deterioration in the patient's condition occurred. The effect of BAL in Case 5 was difficult to assess, as in this case the disease took a very prolonged course, with mainly psychotic features, which varied in severity before treatment was commenced. Furthermore, after the first course of BAL, oral EDTA treatment was given continuously during the intervals. During the first two BAL courses the boy's psychotic state became rapidly worse, but later his father (a doctor) reported that his clinical state had remained more or less stationary for a few months. As he was treated as an out-patient, only a limited number of 24-hour urine collections were practicable, but the serum-copper level was repeatedly estimated, and was markedly altered by BAL (Fig 3). From a fairly even value of 65 μg. per 100 ml. it dropped during the first few days of a BAL course to 35 μg. per 100 ml., and gradually rose during the next three or four weeks to its initial level. This decrease in serum copper under BAL therapy seemed to coincide with the initial rise in urinary copper excretion, and has been observed in other patients.

2. *Molybdenum.* The logical basis for molybdenum administration was the observation of Dick and Bull (1945) that animals grazing on pasture rich in

molybdenum developed signs of copper deficiency; there was a concomitant decrease of the copper concentration in the liver (see also reviews by McElroy and Glass, 1950; Marston, 1952). We therefore felt that there was a hope of removing copper from our patients by oral administration of ammonium molybdate, and the risk appeared slight, as earlier animal experiments suggested a low toxicity for this heavy metal (Fairhall, 1945). Molybdenum was given to four patients (Nos. 1, 4, 6, and 7). For four, six, and 11 months respectively the three last-mentioned patients received molybdenum as their only treatment, while patient No. 1 was given molybdenum for six months with intermittent BAL courses. In Cases 1 and 6 there was no improvement, and in Case 4

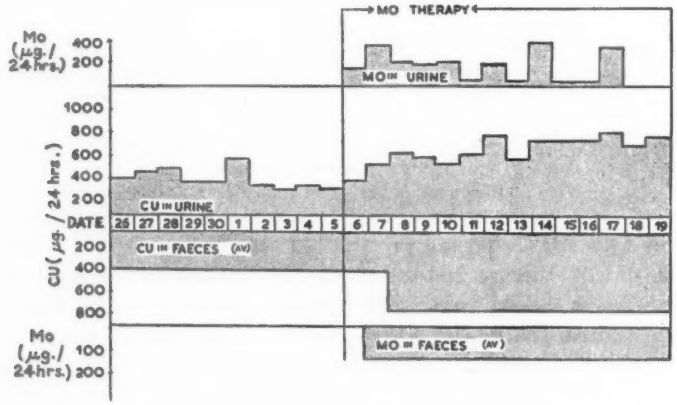


FIG. 4. Copper excretion in a patient treated with molybdenum (Case 1).

deterioration, during this treatment. Only patient No. 7, an extremely unmanageable psychotic girl who had to be nursed in a mental hospital, seemed during the first nine months of molybdenum therapy to become more sensible and co-operative, but she relapsed rapidly when molybdenum was withheld for two months; these variations, however, may have been due to the fluctuating course of the disease. Copper excretion in the urine and stools under molybdenum therapy was followed for a limited period in Cases 1, 4, and 6, but this was not possible in Case 7 because of the violent behaviour of the patient. Fig. 4 shows the findings in Case 1. There was an increase of about 50 per cent. in the urinary copper excretion, and of nearly 100 per cent. in the faecal copper, the single estimations of which had to be averaged because the boy was rather constipated. Very similar results were obtained in Case 4, whereas in Case 6 there was no change in the excretion of copper during two weeks' treatment. The lack of response in this case may possibly have been due to insufficient inorganic sulphate (see page 535), though it was noteworthy that in this patient oral EDTA also remained without effect on the copper excretion (see Fig. 8). In Case 1, besides the copper estimations, the intake and output of molybdenum were estimated. During treatment there was a retention of up to 20 per cent. of the intake of molybdenum. Though no toxic effects were observed, we finally

abandoned this treatment, partly because of its clinical ineffectiveness, and partly from fear of the cumulative effect of molybdenum retention.

3. *EDTA* and its salts are powerful chelating agents of polyvalent metallic ions. The non-ionized complexes so produced are in general soluble, exceptionally stable in slightly alkaline solution, and rapidly excreted. Their toxicity depends on the toxicity of the metal chelated and on the result of competitive reaction for it in the body. Chelates of the transition elements and heavy metals

TABLE V

Copper Balance Study in Case 6 during EDTA ('Versene') Therapy

	Copper intake (3-day mean) (μg./day)	*Copper excretion (μg./day) (3-day mean)*		
		Stool	*Urine*	*Total*
Control period . . .	1,713	1,176	605	1,781
Oral EDTA 1·125 gm./day .	1,827	1,103	743	1,846
Intravenous EDTA 2 × 1 gm./day	1,613	1,022	867	1,889

TABLE VI

Influence of EDTA ('Versene') Therapy on Urinary Excretion of Copper

Case number	*Method of administration*		
	Oral	*Intravenous*	*Intramuscular*
1	++	+++	..
2	+++	..	..
4	No response	..	..
5	No response	..	..
6	No response	+++	+++
10	++	+++	+++

++ = Urinary copper output approximately doubled.
+++ = Urinary copper output approximately trebled.

are more stable than those of the alkaline earths or alkali metals, and are formed when free ions of the former are mixed in solution with chelates of the latter; for this reason, as already mentioned, to chelate copper ions, the calcium disodium salt of EDTA was used throughout. We used EDTA ('versene') in six patients (Cases 1, 2, 4, 5, 6, and 10), and studied its effect on urinary copper excretion after oral and parenteral administration. In one patient (Case 6) a copper-balance study was carried out before and during its administration (Table V); the dosage and mode of application are given on page 535. In our experience the effect of oral EDTA on urinary copper output is variable. A definite increase of the copper excretion in Cases 1, 2, and 10 stands in contrast to the absence of response in Cases 4, 5, and 6. This variation appears, in part, to be due to differences in the patients' ability to absorb EDTA. Foreman and Trujillo (1954) reported that in normal individuals only 5 per cent. of a dose of carbon-labelled 'versene' was absorbed. Parenteral administration in Cases 1, 6, and 10 always resulted in a prompt and substantial increase of urinary copper, which was sustained as long as dosage continued. No toxic reaction was observed in any patient, nor was there any definite clinical improvement under treatment with EDTA. The influence of EDTA administration on copper excretion is summarized in Table VI; further details are as follows:

Case 1. Oral EDTA caused a rise in the urinary excretion of copper, which increased still further after intravenous EDTA (Fig. 5). The interpretation of these results is complicated by the fact that a course of BAL was terminated only a few days before the beginning of the base-line period, and this circumstance may have led to some depression of the initial copper values in the urine

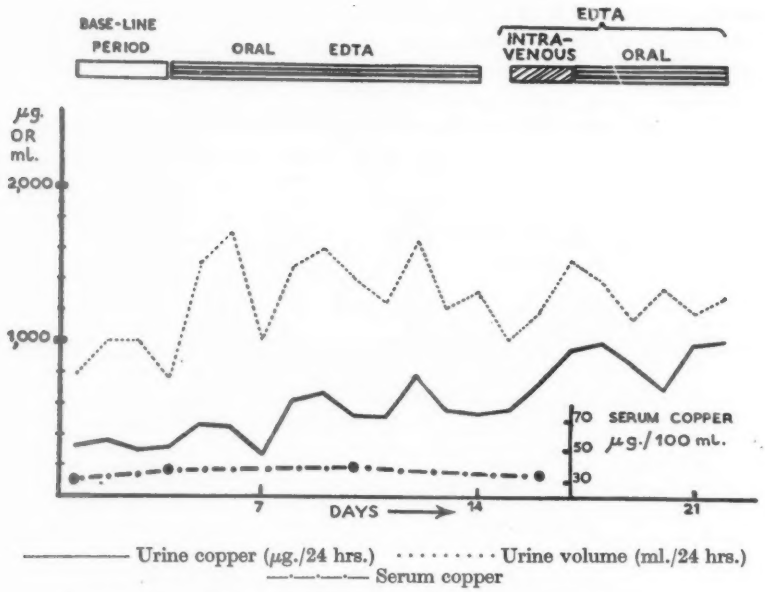


FIG. 5. Effect of oral and intravenous EDTA on urinary copper excretion in Case 1.

and serum (see page 539); it may also explain the fact that the serum-copper level rose instead of falling when EDTA was being given orally. With intravenous EDTA, however, there was a decrease of the serum-copper level coinciding with the increased urinary excretion of copper; but in spite of EDTA therapy the patient deteriorated clinically.

Case 2 showed an exceptionally prompt and striking increase in urinary copper output with oral administration of EDTA (Fig. 6). Three months before the base-line period the patient still had no aminoaciduria, and only mild cupruria, which at the time of commencement of EDTA treatment had risen to 1 mg. of copper per day, together with a marked aminoaciduria. After oral EDTA the copper excretion was more than trebled, but unfortunately our estimations were interrupted by the patient's departure from hospital. At home she continued to take 'versene' tablets, and a month later the high copper excretion was still maintained, though at a reduced level. In spite of therapy, however, the patient grew slowly worse and died two years later.

Case 4. This boy was the first of our patients to receive oral EDTA, and we observed in his urine the changes of frothiness and smell to which reference will be made later. Urinary copper excretion showed no rise (Fig. 7). This might have been due to depletion of more easily removable copper stores during prolonged molybdenum treatment, which had ceased but three weeks previously

and might also have accounted for the irregularities at the beginning of the base-line period. No favourable clinical response was observed.

Case 5. This man was treated only as an out-patient; he had already received BAL treatment, and it was continued in 20-day courses alternately with courses

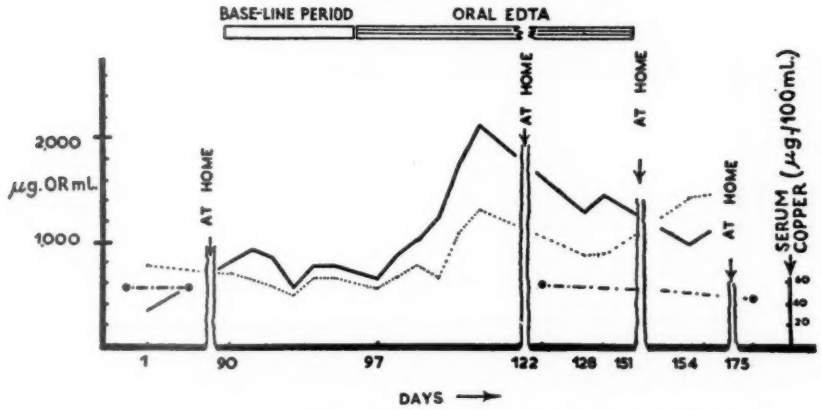


FIG. 6. Effect of oral EDTA in Case 2.

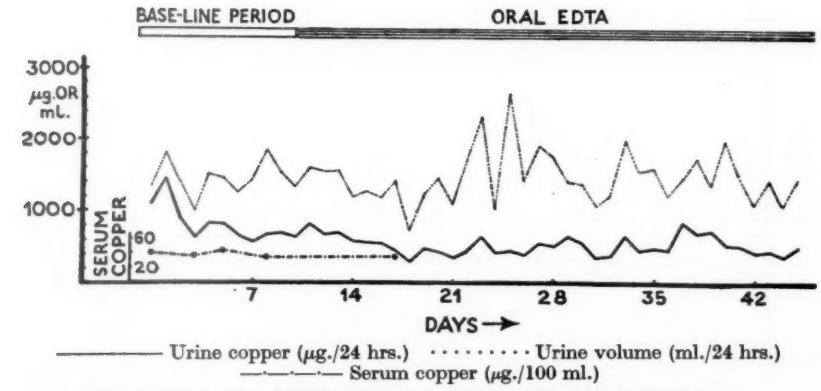
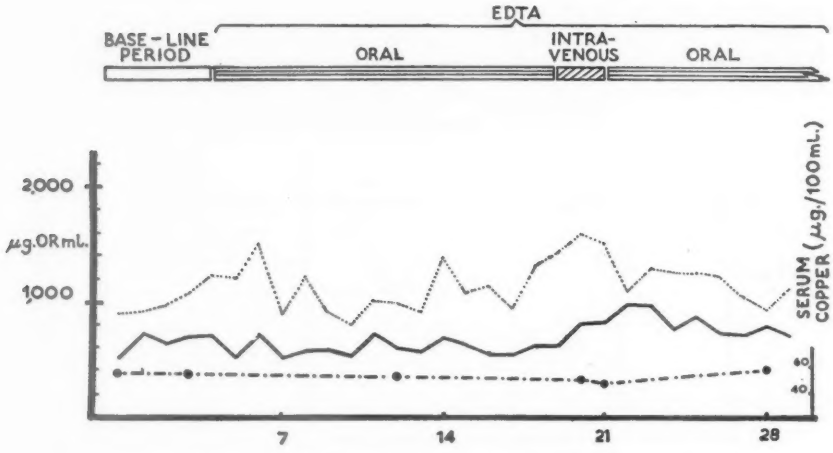


FIG. 7. Effect of oral EDTA on urinary copper excretion in Case 4.

of EDTA by mouth. Under these conditions it was not to be expected that the relatively milder action of oral EDTA would be detectable in the excretion of copper, and indeed no significant changes occurred (Fig. 3).

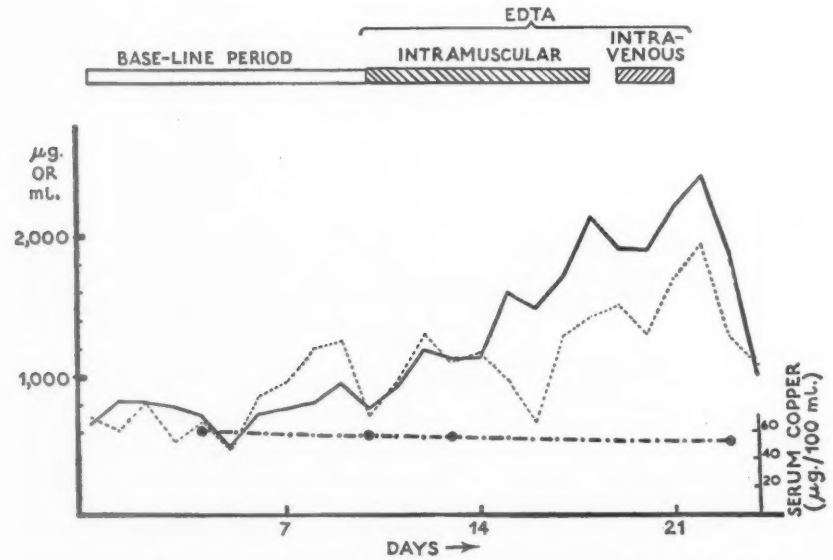
Case 6. Here also there was no increase of urinary copper excretion after oral EDTA (Fig. 8); a balance experiment showed that faecal copper excretion also remained unchanged. Intravenous EDTA, however, caused an immediate rise of copper excretion in the urine, while faecal excretion remained substantially unaltered (Table V). The patient was subsequently given EDTA intramuscularly, with the excellent response shown in Fig. 9; nevertheless, there was no clinical improvement.

Case 10. This patient was still untreated, and therefore particularly suitable



——— Urine copper (μg./24 hrs.) ····· Urine volume (ml./24 hrs.)
—·—·—·— Serum copper

FIG. 8. Effect of oral and intravenous EDTA on urinary copper excretion in Case 6.



——— Urine copper (μg./24 hrs.) ····· Urine volume (ml./24 hrs.)
—·—·—·— Serum copper

FIG. 9. Response to intramuscular EDTA in Case 6.

for therapeutic evaluation. Under oral treatment with EDTA his urinary copper output doubled, and was further increased when the drug was given intravenously (Fig. 10). Intramuscular EDTA kept the copper output at a sustained high level (Fig. 11). During this period the serum-copper level, which

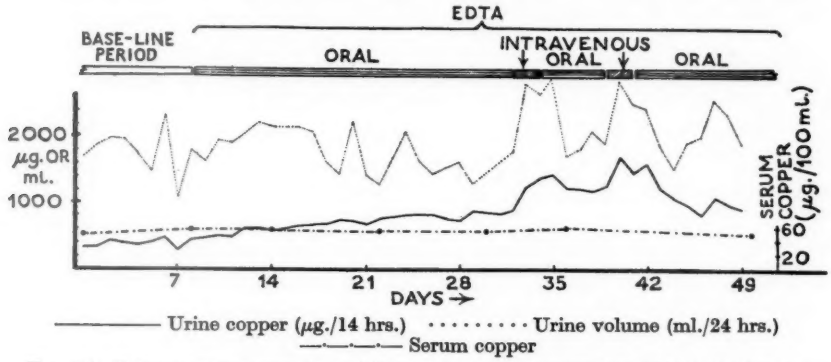


FIG. 10. Urinary copper excretion following oral and intravenous EDTA in Case 10.

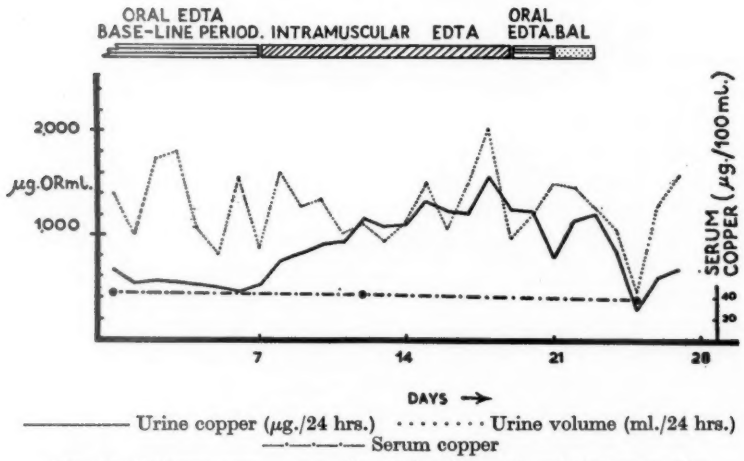


FIG. 11. Urinary copper excretion following oral and intramuscular EDTA in Case 10.

before treatment had been 57 μg. per 100 ml., fell gradually to 42 and 38 μg. per 100 ml., and after about five months' treatment with 'versene' tablets at home was 43 μg. per 100 ml., still well below its initial level. This reduction probably reflects the removal of some of the more accessible copper and a decrease in the circulating non-coeruloplasmin copper, and resembles similar decreases in the serum level under the influence of BAL. In spite of this energetic and prolonged removal of copper by EDTA, no clinical improvement was detected, though no further progression of the disease was observed.

Finally, mention must be made of two observations made on the urine of patients receiving EDTA. One is the marked reduction in frothiness. All our

TABLE VII

Chromatographic Findings in Urine of Patients with Wilson's Disease

*Size and intensity of spots in taurine units (μg.)**

	Case												Average	
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*Patients*	*Normal*
Glycine	> 60	15	—	> 60	30	> 60	> 60	> 60	10	30	> 60	40	55	12·4
Glutamine	40	5	5	> 60	60	20	> 60	> 60	10	30	> 60	10	45	3·5
Histidine	20	5	10	60	50	15	10	> 60	—	15	60	5	28	2·9
Alanine	20	10	8	30	15	10	40	> 60	10	30	30	10	25	3·9
Serine	40	—	3	20	40	30	10	> 60	—	30	30	5	25	0·4
Threonine	10	—	—	20	15	15	15	> 60	—	8	40	—	18	—
Cystine	5	5	10	> 60	30	—	10	10	30	10	10	2	18	1·0
Tyrosine	10	—	5	60	3	10	5	20	—	5	60	—	15	0·08
Lysine	2	—	—	30	30	—	10	60	5	5	20	—	13	0·2
Glutamic acid	—	—	—	—	—	5	—	—	20	10	30	2	6	4·8
Leucines	2	—	3	5	15	—	5	5	—	3	30	—	6	0·13
Phenylalanine	5	—	—	5	3	10	5	5	—	—	30	—	5	0·06
Valine	2	—	3	5	5	—	5	5	—	3	25	—	4	0·18
β-aminoisobutyric acid	10	—	—	—	—	5	—	—	—	—	5	—	2	0·8
Tryptophan	—	—	—	—	—	—	—	2	—	—	10	—	1	—
Methionine-sulphone	—	—	—	—	—	—	—	—	—	—	5	—	0·5	—
Taurine	—	—	—	—	—	—	—	2	—	3	—	—	0·5	0·5
Total T-values	256	40	47	505	296	210	295	649	85	182	565	74	267	31 (0–95)

* T-values; > 60 calculated as 90.

patients, when untreated, passed urine which produced a dense froth on boiling with acid. This froth may have some connexion with the presence of a glycoprotein which can be demonstrated by paper electrophoresis. The second is the rapid production of large quantities of hydrogen sulphide in unpreserved urine standing at room temperature. Preliminary experiments suggest that the hydrogen sulphide is produced by coliform organisms (Dr. H. Smallwood). Its production is enhanced by EDTA and accompanied by a decline in the concentration of cystine. This strong smell of hydrogen sulphide was regularly found in unpreserved specimens of urine from patients receiving intravenous EDTA, and occasionally from patients taking EDTA by mouth; specimens preserved with chloroform and acetic acid failed to produce hydrogen sulphide.

Aminoacid metabolism. Numerous chromatographic investigations of urine and plasma were carried out in the 12 cases summarized in Table I. On the whole the urine showed a characteristic aminoacid pattern, with minor variations from case to case and in the different stages of the disease. A representative chromatogram of Case 1 is given in Fig. 12 (Plate 46), and the findings in all 12 cases are summarized in Table VII. Compared with chromatograms of normal urine and of other types of aminoaciduria, there is a marked increase of threonine, cystine (as cysteic acid), serine, and tyrosine, and also of glycine, alanine, glutamine, and histidine, which are nearly always present in small amounts in normal urine. Less marked and regular was the increase of valine, the leucines, and phenylalanine, and sometimes of glutamic and aspartic acids. Lysine was increased in the urine of seven patients, and sometimes there was an increase of methionine (as sulphone) and of tryptophan. In three patients chromatographic investigations of many urine specimens during months and years showed no aminoaciduria. Two of them (Cases 2 and 3) seemed well, except for liver enlargement, while the third (Case 12) showed no mental and little neurological involvement, but suffered from advanced liver atrophy and showed abnormal results in liver-function tests. The hepatic changes in these patients therefore could not have been due to loss of aminoacids in the urine. Furthermore, one patient (Case 6) showed marked aminoaciduria without any neurological involvement, suggesting the absence of any direct relationship between these features of the disease. In general, however, there was little variation in the level of the aminoaciduria for months at a time, though we followed its gradual development in a young patient (Case 2), its increase in patients under observation for several years, and finally its decrease in the terminal stages of the disease (Case 9). Differences in the aminoacid excretion cannot be explained by variations in the food taken by our patients, as they all received the usual hospital diet, with the exception of two (Cases 9 and 12) whose anorexia may have contributed to the decrease or absence of aminoaciduria. Increase of the cupruria after BAL, molybdenum, or EDTA had no influence on the level of the aminoaciduria, whereas Matthews, Milne, and Bell (1952) and Stein, Bearn, and Moore (1954) showed that a diet rich in aminoacids or protein led to an increase not only of the aminoaciduria but also of the cupruria.

TABLE VIII

α-Aminoacid Nitrogen in Plasma and Urine of Patients with Wilson's Disease

(Gasometric ninhydrin method)

	Case						
	1	*2*	*4*	*6*	*7*	*10*	*Normal range*
α-Amino nitrogen:							
In plasma (mg./100 ml.)	3·8–5·1	4·4	3·9–5·4	2·9–4·0	3·7	4·0	3·5–5·3
In urine (mg./24 hrs.) .	282–456	197	..	168–392	..	144–326	100–150

TABLE IX

Aminoacid Levels in Plasma (Microbiological Assay)

Case number	*Phenylalanine*	*Tyrosine*	*Tryptophan*	*Valine*	*Lysine*	*Arginine*
1	1·8–3·0	1·7–4·8	1·2–2·1	2·7–6·0	..	..
	av. 2·4 (7)*	av. 2·5 (9)	av. 1·55 (4)	av. 3·9 (4)		
2	2·1	1·6	1·1	2·9	..	..
4	1·25–1·8	1·6–2·4	0·8–1·6	2·9–3·0	4·0	2·4
	av. 1·5 (3)	(2)	av. 1·15 (5)	(2)		
6	1·3–2·1	1·4–2·0	0·8	3·0	2·9	2·2
	av. 1·6 (4)	av. 1·8 (3)	(2)			
7	1·4–2·7	1·8–3·2	1·1–1·6	2·9–4·8	3·0	..
	av. 2·15 (4)	av. 2·4 (4)	av. 1·3 (4)	av. 3·6 (4)		
8	2·1–2·15	1·0–1·5	..	..	..	..
	(2)	av. 1·3 (5)				
9	0·7–1·4	0·8–1·3	0·7–1·05	2·8–3·2	2·6	2·4
	(2)	(2)	(2)	(2)		
10	1·0	..	..	..	..	..
11	3·9	3·5	..	2·9	..	..
Normal average†	1·38	1·48	1·08	2·83	2·95	2·34

* The figures in parentheses indicate the number of specimens tested.
† Krebs (1950).

TABLE X

Aminoacid Excretion in Urine (Microbiological Assay)

(mg. per 24 hours)

Case number	*Phenylalanine*	*Tyrosine*	*Tryptophan*	*Valine*	*Lysine*
1	68·4–467	156–250	174	12·5	..
	av. 271 (6)*	av. 220 (4)			
2	14·6	51·6	1·3	17·2	..
4	13·4–59·6	322	36–94	20·1	98–509
	(2)		(2)		(2)
6	56	..	..	..	..
8	90–124	151–6			
	av. 105 (5)	(2)	..	..	..
Normal excretion†	7·5–34	10·5–43·9	8·5–56·0	0–7·5	18·2–88·2

* The figures in parentheses indicate the number of specimens tested.
† Woodson, Hier, Solomon, and Bergheim (1948).

The aminoacid pattern of plasma chromatograms was examined in seven patients, and found to be normal. As paper chromatography is only a semi-quantitative method, and is incapable of detecting minor variations, especially

of the concentration found in plasma, α-amino nitrogen was estimated in numerous plasma and urine specimens of six patients by the gasometric ninhydrin method (Table VIII). Whereas the plasma levels all fell within the normal range, there was an increase up to fourfold of the α-amino nitrogen excretion in 24-hour specimens of urine.

Some individual aminoacids were estimated quantitatively in plasma and urine by microbiological assay (Tables IX and X). Nearly all the aminoacid plasma levels were within the normal range, except for some tyrosine, phenylalanine, and valine values in Cases 1, 7, and 11, which were at the upper limit of normal or slightly above it.

Glycosuria. In 11 of the 12 patients Benedict's reaction and sugar chromatography were performed on several 24-hour urine collections; in Case 2 only a single non-fasting sample of urine was available. Only in Cases 7 and 10 was a green colour reaction repeatedly observed; all other cases showed a blue or blue-green reaction. Qualitative and semiquantitative evaluation of the urine by chromatography showed that in Case 7 the patient excreted about 200 mg. of glucose per 100 ml.; his fasting blood-sugar was normal. In Case 10 traces of glucose (20 mg. per 100 ml.) were detected, such as are found in chromatograms of normal urine (Bickel and Souchon, 1955). Traces of glucose, galactose, and lactose were found in several other cases, and were probably not abnormal. It is not certain whether fructosuria in Cases 2 and 5 (50 mg. per 100 ml.) and Case 11 (60 mg. per 100 ml.) was within the normal range. This glycosuria may have been nutritional in origin, but a similar or more pronounced excretion of fructose, often combined with moderate glucosuria, galactosuria, and lactosuria, was also repeatedly observed in patients with other severe liver disorders (Bickel and Souchon, 1955).

Discussion

Diagnosis. Existing knowledge of the underlying metabolic error suggests that early diagnosis—not always possible on clinical grounds alone—offers the best hope of arresting the disease. The most important and only pathognomonic clinical sign is the Kayser-Fleischer ring, which, if well defined, permits of immediate diagnosis despite otherwise ill-defined clinical features (Case 6). In the second youngest patient of Markowitz, Gubler, Mahoney, Cartwright, and Wintrobe (1955) the ring was still absent in spite of the presence of dysarthria, tremor, and characteristic copper changes in the blood and urine; and Blaha, Gastager, Tschabitscher, and Wewalka (1954) recorded a similar experience (compare our Cases 2 and 3). Indeed, it may be said that no clinical sign is absolutely reliable, and therefore additional techniques may have to be employed in diagnosing the early case. Figs. 1 and 2 illustrate the fact that hypocupraemia and cupruria were present in every one of our patients. While cupruria is generally recognized as an essential feature of the disease, the serum-copper level has until recently been reported to be high or normal. Bearn and

Kunkel (1952) and Bearn (1953) were the first to publish consistently low serum-copper levels (in 15 of their 16 patients), and this finding has since been confirmed by Lahey, Gubler, Brown, Smith, Jager, Cartwright, and Wintrobe (1953), Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe, and Bean (1954), Gastager, Hornykiewicz, and Tschabitscher (1954), Hornbostel (1954), Zimdahl, Hyman, and Stafford (1954), Markowitz, Gubler, Mahoney, Cartwright, and Wintrobe (1955), Bush, Mahoney, Markowitz, Gubler, Cartwright, and Wintrobe (1955), and others; there can be little doubt that most of the high serum-copper levels that have been reported were due to contamination, which can so easily occur in the estimation of this trace metal. For some normal or high values, however, especially those recorded by experienced workers in this field, Cartwright's explanation may hold true. This is based on the observation by Scheinberg and Gitlin (1952) and Bearn and Kunkel (1952) that coeruloplasmin, a laccase, which normally contains about 90 to 96 per cent. of the total serum copper, is deficient in the blood of these patients. Cartwright and his collaborators (1954, 1955) showed that, while this decrease of oxidase activity corresponds to a similar decrease of coeruloplasmin-bound copper, the copper not so bound is increased. As a rule even a multifold increase of this relatively small copper fraction will not outweigh the considerable fall in the level of coeruloplasmin copper, but an occasional exception is conceivable, and may result in an increased total serum-copper level. Thus two of Markowitz's patients, with normal or nearly normal total serum-copper levels (100 and 86 μg. per 100 ml. respectively), nevertheless showed considerably reduced coeruloplasmin levels. To our knowledge no patient suffering from hepatolenticular degeneration has yet been found without this reduction in the blood coeruloplasmin level and without cupruria. Unfortunately coeruloplasmin levels were not estimated in our patients, but the low serum-copper levels, even in the very early Cases 2 and 3, can only have been due to coeruloplasmin deficiency, which, together with cupruria, seems to be the earliest biochemical sign of the disease. It should be added that according to Cartwright, Gubler, and Wintrobe (1954) and Markowitz, Gubler, Mahoney, Cartwright, and Wintrobe (1955) the nephrotic syndrome also exhibits a reduced coeruloplasmin level in the blood, hypocupraemia, and cupruria, which are due to a leak of coeruloplasmin through the kidney, whereas in Wilson's disease no coeruloplasmin was detected in the urine by these authors.

Aminoaciduria was found in nine of our 12 patients. The demonstration of the aminoacid pattern in the urine by paper chromatography proved of greater diagnostic value than the quantitative estimation of the α-amino nitrogen, and helped to differentiate this aminoaciduria from that due to other causes (Bickel, 1952, 1953, 1954; Bickel and Souchon, 1955). De Verdier (1950), Dent and Harris (1951–2), Matthews, Milne, and Bell (1952), and Blaha, Gastager, Tschabitscher, and Wewalka (1954), using paper-chromatographic methods came to similar conclusions. Cooper, Eckhardt, Faloon, and Davidson (1950) employed microbiological assay, and Stein, Bearn, and Moore (1954) used column chromatography to obtain quantitative estimations of various individual

aminoacids, but these methods, though of great interest in research, are of limited diagnostic value, as they are too involved for routine use. In three of our 12 patients no aminoaciduria was detected, in spite of repeated investigations during many months. Blaha, Gastager, Tschabitscher, and Wewalka (1954) found no aminoaciduria in one of eight patients; patients without aminoaciduria were also reported by Cooper, Eckhardt, Faloon, and Davidson (1950), Cumings (1951), Bearn and Kunkel (1954*b*), Stein, Bearn, and Moore (1954), and Markowitz, Gubler, Mahoney, Cartwright, and Wintrobe (1955). This strongly suggests that aminoaciduria is neither the expression of an inborn error of protein metabolism, nor the cause of the liver cirrhosis, as was suggested by Uzman and Hood (1952), Brick (1952), Jervis (1952), Uzman (1953), and Denny-Brown (1953). Furthermore, from the absence of aminoaciduria in our Case 12, with severe liver involvement, it may also be deduced that liver disturbance is not a principal cause of aminoaciduria. In our two youngest patients, as well as in the second youngest patient of Markowitz, Gubler, Mahoney, Cartwright, and Wintrobe (1955), the absence of aminoaciduria was probably due to the fact that it is a secondary feature, developing after some delay, and in no way excludes the diagnosis of Wilson's disease.

Pathogenesis. The pathogenesis of this complex metabolic disorder is still far from clear. An increase of the copper content of various organs is illustrated in Table II, and has repeatedly been reported (for references see Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe, and Bean, 1954; Schreier, 1955). Our balance results (Table III), as well as those of Zimdahl, Hyman, and Cook (1953) and Cartwright and his colleagues (1954), show that this accumulation of copper is associated with a reduced faecal copper output, which may be due to increased absorption from or decreased excretion into the intestine, or both, and balance studies cannot determine which of these disturbances is present. Experiments with intravenously administered radioactive copper, however, undertaken by Bearn and Kunkel (1954*b*, 1955), Earl, Moulton, and Selverstone (1954), Matthews (1954), Bush, Mahoney, Markowitz, Gubler, Cartwright, and Wintrobe (1955), and unpublished observations by Quinton, Neale, and Bickel, provide evidence that there is a decreased excretion into the intestine. The cause and mechanism of this decreased excretion, if it exists, remain unexplained. Indeed, its very existence has been disputed on the grounds of a normal biliary copper concentration found in three of Denny-Brown and Porter's patients (1951) and in one patient of Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe, and Bean (1954). In health the copper concentration of duodenal bile obtained by intubation seems to show a very broad range, 35 to 205 μg. per 100 ml. (van Ravesteyn, 1944). We have insufficient knowledge of the copper content of 'gall-bladder' bile of the healthy person, and it presumably varies with the concentration of the bile itself. Furthermore, according to van Ravesteyn, copper is excreted not only via the bile but also directly through the intestinal wall, and we therefore think it unwise to draw any firm conclusion from the biliary values in Cases 2 and 9 (Table II).

After absorption from the intestine the copper, perhaps because of an inborn

defect in coeruloplasmin synthesis (Scheinberg and Gitlin, 1952; Scheinberg, Dubin, and Harris, 1955) is mainly bound in a looser form to the serum-albumin (Bearn and Kunkel, 1954*a*, 1955; Earl, Moulton, and Selverstone, 1954; Bush, Mahoney, Markowitz, Gubler, Cartwright, and Wintrobe, 1955), and to the proteins of various organs. The diffusible copper which is excreted in the urine has probably been dissociated from this copper-albumin complex during its passage through the kidneys (Bearn and Kunkel, 1955). Furthermore, Earl, Moulton, and Selverstone (1954) have shown that a small but definite fraction of ^{64}Cu added *in vitro* to normal plasma or to that of a patient suffering from Wilson's disease will pass a cellophane membrane, and could thus presumably also pass the glomerular membrane of the kidneys. Considering the concentrating power of the kidney, only a small increase of this diffusible fraction would be necessary to account for the cupruria of Wilson's disease (Matthews, Milne, and Bell, 1952). In this connexion it is of interest that Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe, and Bean (1954) found increased copper concentration in the cerebrospinal fluid of all their six patients tested; this copper was not bound in coeruloplasmin, whereas in a control group about one-half of the spinal-fluid copper was so bound. Part of the copper deposited in the tissues must also be rather loosely bound, as it can easily be mobilized by copper-removing agents; some preliminary analyses for coeruloplasmin, undertaken by Markowitz, Gubler, Mahoney, Cartwright, and Wintrobe (1955) showed, despite a multifold increase of copper, a reduced oxidase activity of the liver and kidneys as compared with the normal.

The biochemical data in Cases 2 and 3 suggest that the aminoaciduria is secondary to the disturbance of copper metabolism. It may be recalled that aminoaciduria has also been observed in lead poisoning (Wilson, Thomson, and Dent, 1953; Chisolm, Harrison, Eberlein, and Harrison, 1955; Bickel and Souchon, 1955). The pattern of the aminoaciduria in these two conditions is very similar, and suggests a common mechanism, namely, damage of the tubular function by heavy metals. The occurrence of renal glycosuria, which has been repeatedly described in lead poisoning (for references see Wilson, Thomson, and Dent, 1953) and in hepato-lenticular degeneration (Cooper, Eckhardt, Faloon, and Davidson, 1950; Bearn and Kunkel, 1954*b*; Case 7 of the present series), points in the same direction. The renal mechanism of this aminoaciduria is also indicated by the fact that all the α-amino-nitrogen values, and most levels of the individual aminoacids, in the plasma of our patients were normal (Tables VIII, IX, and X). Similar conclusions were reached by Cooper, Eckhardt, Faloon, and Davidson (1950), Matthews, Milne, and Bell (1952), and Stein, Bearn, and Moore (1954), but the last-mentioned authors, in evaluating plasma-aminoacid levels by column chromatography, remarked on the fact that failure of tubular reabsorption could not account for all their findings, such as the diminished excretion of several aminoacids, for example taurine and methylhistidine. Cooper, Eckhardt, Faloon, and Davidson (1950) found in the plasma of their patients a moderate increase of some α-amino-nitrogen values, and Matthews, Milne, and Bell recorded in their second patient 6·9 mg. per 100 ml.,

which is definitely above normal for the gasometric ninhydrin method used. Some of our plasma values for phenylalanine, tyrosine, and valine seem also to be above the normal range. In the urine chromatograms of some of our patients with advancing liver destruction we repeatedly observed methionine and tryptophan, a characteristic finding in severe liver damage. We suggest therefore that, though the mechanism of aminoaciduria in Wilson's disease is mainly renal, prerenal and probably hepatic factors may also develop as the disease progresses.

Considering the results of our own investigations and on those of other workers, we suggest the following simplified hypothesis concerning the pathogenesis of this disorder. There is a congenital, genetically determined deficiency of coeruloplasmin, with an increase in the circulating non-coeruloplasmin copper—probably 'transport' copper bound to albumin—leading to its deposition in the tissues and increased urinary excretion of the metal. In the course of years accumulation of copper causes damage to the brain, liver, and kidneys. Copper excretion into the intestine is decreased as a result of retention of the metal in the tissues and its loss in the urine, and perhaps also because the excretory mechanism through the liver and bile is disturbed. If this is accepted as a working hypothesis, efforts to prevent or relieve copper accumulation in the body and, if possible, to combine this with replacement therapy with coeruloplasmin, would seem to be the best form of treatment at present available.

Treatment. Until very recently coeruloplasmin was not available for this purpose, but in 1954 Professor Schultze of the Behringwerke in Marburg, Germany, provided one of us (H. B.) with sufficient to initiate treatment. So far three patients have been given repeated intravenous infusions of coeruloplasmin (Bickel, 1955; Bickel, Schultze, Grüter, and Göllner, 1956). At first serious side effects such as circulatory collapse were encountered, but these have since been overcome, and the coeruloplasmin content, oxidase activity, and copper level in the serum have been restored to normal values over a period of months. It is, however, still too early to draw any conclusions as to the clinical effect of this new therapeutic approach. The biological importance of copper as the prosthetic group of various enzymes is well established (Holmberg and Laurell, 1951; Wolff, 1952), though in rats copper deficiency for two generations did not influence normal cerebral development (Frick and Lampl, 1953). The role of coeruloplasmin and the fate of the copper bound in it are still obscure; it is possible that their marked reduction is of pathological significance in Wilson's disease, quite apart from the damaging effect of copper deposition in the tissues. In this connexion it should be borne in mind that administration of coeruloplasmin containing about 0·32 per cent. of copper (Holmberg and Laurell, 1948) means that with each gramme of protein 3·2 mg. of copper are also introduced. Ideally the injection of the protein moiety alone, provided that the resynthesis of the complete enzyme within the patient results, would seem to be the goal.

On this hypothesis, however, certain of our recent observations are difficult to understand. A very low serum-copper level (45 μg. per 100 ml.) was found in

the father of two of our patients (Cases 2 and 8), and a marked reduction (71 μg. per 100 ml.) in the mother. A somewhat reduced level (84 μg. per 100 ml.) was also established in the father of two other patients (Cases 6 and 10), although the mother showed a high normal value (147 μg. per 100 ml.); moreover, the eldest child (clinically unaffected) in the same family also had the low level of 72 μg. per 100 ml. It is noteworthy that Markowitz, Gubler, Mahoney, Cartwright, and Wintrobe (1955) have recorded 68 μg. per 100 ml. in one subject among a control group of 228 persons. Preliminary immunochemical investigations, carried out in collaboration with our colleague Dr. P. G. H. Gell, have disclosed a pronounced deficiency of coeruloplasmin in these specimens in which the total copper level is low. These findings are leading us to test further serum-copper and coeruloplasmin levels in other members of affected families, for it is not easy to see why the parents, and in particular the one father, should be clinically unaffected, while their children, with similar copper levels, have died of the disease. All this re-emphasizes our lack of knowledge concerning the role of coeruloplasmin in the pathogenesis of Wilson's disease.

Drugs such as BAL and EDTA have a pronounced copper-removing action. In Wilson's disease BAL has been used extensively for this purpose, and most authors have commented favourably on its use (Denny-Brown, 1953; Streifler and Feldman, 1953; Tyler and Armstrong, 1954; Hornbostel, 1954). With EDTA, on the other hand, there has been much less experience, though after its intravenous use increased cupruria has been described (Bearn, 1953; Bearn and Kunkel, 1954*b*; Zimdahl, Hyman, and Stafford, 1954; Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe, and Bean, 1954). After oral EDTA the same authors reported equivocal results, and so far no clinical improvement has followed its use. Our therapeutic trials of BAL and EDTA agree on the whole with these observations, but we are disappointed by the clinical results of BAL therapy, even after 10 courses of injections given early in the disease (Case 2). This experience is in contrast to the benefit reported in Warnock and Neill's (1954) patient, who was also still in a relatively early stage of the disease. It is surprising that Palmer, Drew, and Chenoweth (1953) found at autopsy a normal copper content in the organs of their patient after only four courses; these results are at variance with the autopsy findings in the patient of Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe, and Bean (1954), and in our Cases 2 and 9, in both of which there was still considerable accumulation of copper in spite of several courses of BAL. Apart from the questionable benefit derived from BAL, its painful intramuscular administration, its toxicity, and its declining effect on copper excretion after less than 10 days, led us to search for other copper-removing agents. Molybdenum proved disappointing, and an extensive trial was therefore given to EDTA ('versene'), which convinced us that for the purpose of copper removal it is more effective than BAL. Given intravenously or, more conveniently, intramuscularly, EDTA does not lose its effect on copper excretion even after months of continuous administration, and no toxic reactions were encountered. Variable absorption probably explains why only three of six patients treated orally responded with increased cupruria.

But, in spite of the excellent removal of copper achieved by parenteral EDTA, no clinical improvement was observed, although one patient (Case 10) was energetically treated for more than 12 months.

No final decision can yet be made as to the value of copper-removing therapy. It may well be, as Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe, and Bean (1954) pointed out, that present-day therapy is not energetic and continuous enough to turn copper balances from positive to negative over a sufficiently long period. To achieve this object daily injections of EDTA for months and years seem to us more promising than BAL therapy with its necessary intermittency. Of the many other agents shown to increase copper excretion in this disease, oral administration of potassium sulphide deserves particularly careful consideration, for Cartwright proved by copper-balance studies that 20 mg. of potassium sulphide, given three times daily with meals, changed a positive into a negative balance by increasing the copper output in the stool. In conclusion, therefore, we suggest that replacement therapy with coeruloplasmin, having now become possible, should be carefully evaluated, though little is at present known about the pathogenic effects of coeruloplasmin deficiency. Energetic copper depletion might be achieved if continuous daily treatment with intramuscular EDTA, combined with oral potassium sulphide, could be enforced for a very long period. A diet rich in protein (Bearn and Kunkel, 1954*b*), and avoidance of copper-rich foods, may further help in preventing accumulation of copper in the organs. The most fruitful field for therapy undoubtedly lies in the arrest of the disease in its earliest stages, before irreversible damage is done.

The work on which the present paper is based was made possible only by the unfailing help and interest of many colleagues in Birmingham and elsewhere, for they referred patients to us, co-operated in the investigations, and allowed us access to notes; to all to whom we are indebted we tender sincere thanks. In particular we would mention Dr. E. M. Hickmans, former biochemist of the Birmingham Children's Hospital, for her work reported in the section dealing with molybdenum; Mr. H. B. Salt, her successor, for laboratory and staff facilities; Mr. Garfield Thomas, Biochemist at the Queen Elizabeth Hospital, in whose department many of our investigations were done; Professors P. C. P. Cloake, J. W. Orr, and J. M. Smellie; Drs. Carey Smallwood, H. Smallwood, G. Davison, R. Gaddie, C. M. Ross, F. A. Pickworth, and P. G. H. Gell; Dr. Norman W. Karr, of Rikers Inc., Los Angeles, U.S.A., and Mr. J. A. Lumley of the same firm in this country, for making available to us generous gifts of 'versene'; Dr. H. S. Baar, for invaluable help in the pathological aspects of this study; and Professor J. R. Squire, for stimulating criticism in the preparation of this paper.

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Summary

1. A clinical and biochemical evaluation of Wilson's disease in 12 patients is given.

2. All the patients showed cupruria and reduced serum-copper levels, and the latter abnormalities were also found, without any clinical manifestations, in four near relatives of our patients (two fathers, one mother, and one brother). In the three cases investigated the copper content of various organs was high, and in three cases copper-balance experiments showed a diminished output of copper in the stools; data regarding copper concentration in the bile are difficult to evaluate.

3. Aminoaciduria of a characteristic pattern was present in all but three cases. Normal levels of α-amino nitrogen and of individual aminoacids in the blood suggest a renal mechanism, though occasional raised values, and certain changes in the aminoacid pattern of the urine, indicate that an additional hepatic factor may develop. The similarity of the aminoaciduria to that seen in lead poisoning, and its absence in our two youngest patients, suggest that it is a secondary feature of the disease due to tubular damage by copper. Proteinuria and glycosuria may have a similar origin, though small amounts of other sugars in the urine may be due to liver insufficiency. There is no correlation between aminoaciduria and the degree of damage to the liver or brain.

4. In an extensive trial of copper-removing agents, intramuscular or intravenous 'versene' (EDTA) was more successful than either BAL or molybdenum. When given parenterally, EDTA seems not to lose its copper-removing powers, even after months of continuous administration, nor to produce toxic effects; but when given orally it led to an increased cupruria in only three of six patients. No influence on the aminoaciduria was seen after any of these drugs, nor was any clinical improvement apparent, in spite of prolonged and energetic removal of copper.

5. Our disappointing clinical results may be due to the fact that we failed to produce a negative copper balance for a sufficiently long period. Continuous daily injections of EDTA, combined with oral potassium sulphide and a protein-rich and copper-restricted diet, may achieve this purpose. In addition an attempt should be made, now that this enzyme is becoming available, to correct coeruloplasmin deficiency, for this appears to be an essential feature of the disorder.

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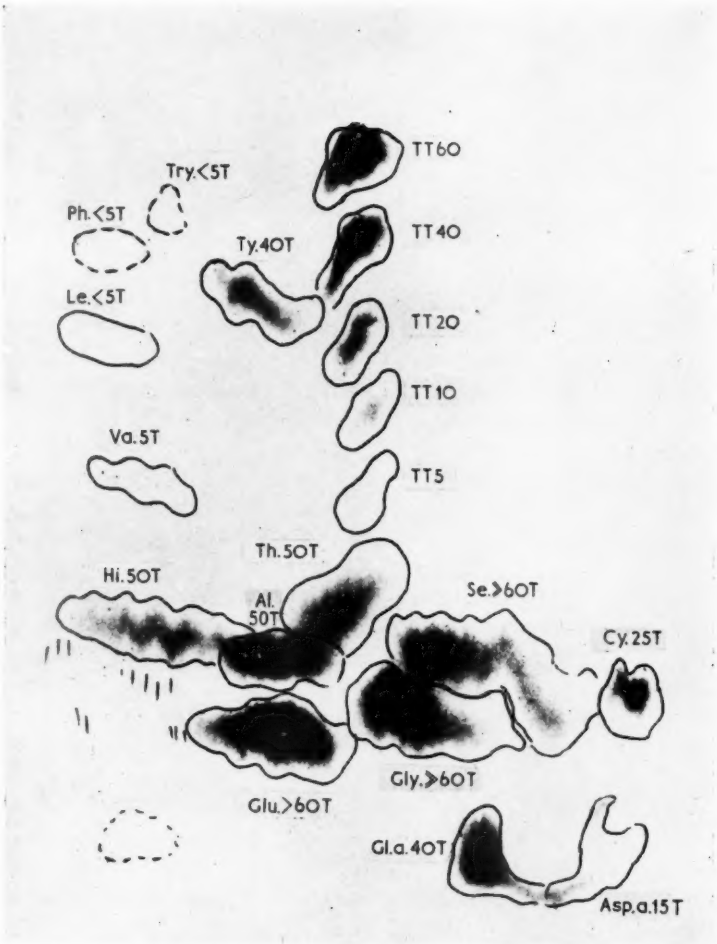

FIG. 12. Aminoacid chromatogram of the urine in Case 1, showing aminoaciduria of typical pattern

Cy. = cysteic acid; Asp. a. = aspartic acid; Gl. a. = glutamic acid; Gly. = glycine; Se. = serine; Th. = threonine; Al. = alanine; Glu. = glutamine; Hi. = histidine; Va. = valine; Le. = leucines; Ph. = phenylalanine; Try. = tryptophan; Ty. = tyrosine. TT = test taurine spots with 5, 10, 20, 40, and 60 μg. taurine. The figures after the abbreviations express the size and colour intensity of the spots in taurine units

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THE IODIDE-REPLETION TEST[1]

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It is now well established that radioiodine tests can reveal the increased rate of iodine metabolism found in hyperthyroidism, as well as the decreased rate found in complete hypothyroidism (Skanse, 1949; Werner, Quimby, and Schmidt, 1949; Pochin, 1950; Fraser, Hobson, Arnott, and Emery, 1953; Wayne, 1954; Rall, 1956). As might be expected, however, similar abnormalities in the test results may occasionally arise either from deficiency of iodine (Stanbury, Brownell, Riggs, Perinetti, Itoiz, and del Castillo, 1954) or from excess of it (Keating, Haines, Power, and Williams, 1950). Such abnormal radioiodine metabolism without thyroid disease is uncommon, but the physician needs some means of recognizing it when it is suspected. He must check the record of drugs recently administered, and see that any test will be independent of them. When, however, abnormal iodine stores are suspected, either from a history of certain recent drugs or from the finding of an abnormal radioiodine uptake not clearly compatible with the clinical picture, some supplementary tests are needed which can check whether the radioiodine abnormalities could arise merely from excessive or defective iodine stores. The test described below provides one such check.

Abnormal results with radioiodine can probably arise only from disorders of thyroid secretion, from the effects of drug administration, or from abnormal iodine stores due to any cause. Thus iodine metabolism in the thyroid will be blocked when the patient is receiving antithyroid drugs, or after he has received either iodine-containing drugs or thyroid extract, and will be rapid after the cessation of some months of administration of antithyroid drugs whose exhibition has led to an iodine deficiency. The cause of some anomalous radioiodine results may be revealed by routine inquiry into recent drug administration. Further, whenever an excess of iodine intake is suspected ('flooding' of the body with iodine), its existence can usually be confirmed by a simple chemical test for excessive urinary iodide (Fraser, Hobson, Arnott, and Emery, 1953) combined with re-testing four weeks later. Unfortunately this test is not sensitive enough for the recognition of iodine deficiency, for the detection of which some other simple test is required. The 'iodide-repletion' test described below has been evolved for this purpose. This test consists, first, in the administration of a standard iodide load which should replace all but the severest of iodine deficiencies. Then, after a standard lapse of time to permit urinary excretion of the

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excess of iodide, any simple radioiodine test is performed. This last test can then assess thyroid function independently of any previous iodine deficiency. The iodide-repletion test should therefore separate patients showing a rapid radioiodine turnover into those in whom this effect was due to iodine deficiency and those in whom it was due to thyrotoxicosis. It thus permits accurate testing of thyroid function in cases suspected of iodine deficiency. It may, indeed, separate all patients showing a 'false positive' avid radioiodine uptake from those in whom the avid uptake is truly confirmatory of thyrotoxicosis. We shall first outline the preliminary observations from which the standard procedure was evolved, and then present the results of a clinical trial of the procedure in 99 patients.

Preliminary Studies on Goitrogen-induced Myxoedema to evolve a Standard Technique for the Test

Little is known of the time required to correct an iodine deficiency, either when the patient is given only an ordinary diet or when he is also given supplementary iodide. The body's normal iodine content of 20 to 50 mg. greatly exceeds the usual dietary intake of iodine (about 100 μg. per day). Thus many months would be required for the unassisted restoration of significant iodine deficiency. For example, assuming a mean retention of as much as 90 per cent. of an average intake of 100 μg. of iodine per day, 200 days would be required to replace a deficiency of 18 mg., or about half of the body's iodine. Clearly, in order to restore any suspected iodine deficiency one should give supplementary iodide. Our preliminary studies were concerned with the optimum dosage and duration of such treatment.

We were able to study these points on certain patients who came to the clinic with myxoedema, which was found to be due to the previous administration of antithyroid drugs or goitrogens given for other reasons (Bull and Fraser, 1950; Balint, Fraser, and Hanno, 1954). In these patients the suspicion of primary thyroid disease did not arise, and their secondary iodine deficiency was clearly severe. Early in these studies it became evident that a single dose of iodide, however large, was insufficient to restore the deficiency. This was presumably because the iodide had first to be synthesized into hormone if it was to be stored in the body; and evidently the duration of the raised iodide level following one dose sufficed only for a fraction of the required synthesis. Fig. 1 records the observations made on one such patient at intervals for a period of 819 days. The initial tests, made six days after stopping the antithyroid drug, gave results characteristic of iodine deficiency: a plasma protein-bound iodine level of under 1 μg. per 100 ml., and an avid uptake of radioiodine (48-hour urinary excretion 6 per cent., with a T index of 90 (Fraser, Hobson, Arnott, and Emery, 1953)). After two months of unsupplemented diet these test results were essentially unchanged. Then, at intervals, three different iodide loads were administered, and their effects on the iodine deficiency observed. The first two, a single dose of 60 mg. and then a series of three daily

doses of 20 mg. of potassium iodide pills, were insufficient for the full correction of the deficiency, as shown by the still subnormal values of plasma protein-bound ^{127}I a fortnight after each dose, and also by the avid radioiodine uptake found later at 258 and 375 days. Full restoration was attained after a final 14-day period of iodide pills (10 mg. daily for 14 days), shown by the subsequent normal results of radioiodine tests one month later, and again over a year later,

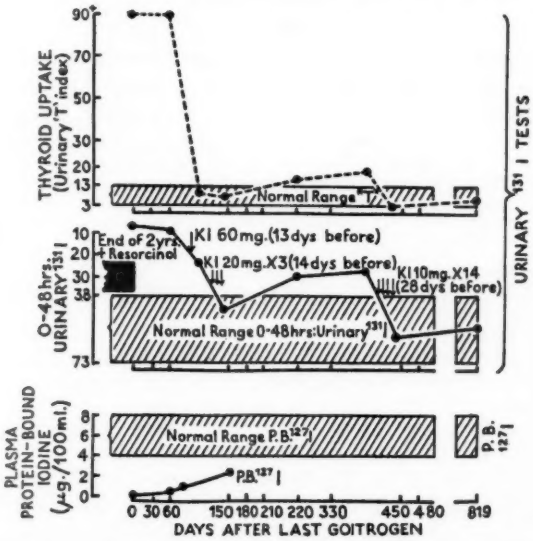

FIG. 1. Iodide-repletion tests in a patient with iodine deficiency due to resorcinol.

at 819 days. From this, and similar detailed studies of three other patients, we concluded that a daily dose of 10 mg. KI, given for either one or two weeks, should be a suitable iodide load for the restoration of most iodine deficiencies. We therefore carried out wider clinical trials with both these durations of iodide loading, and also a few trials with longer periods, the results of which are detailed below. After all these periods of iodide load we found, at the tests made one month later, that almost all of the clinically 'false positive' results with radioiodine returned to normal (see Figs. 2 to 4). In one case, however, an example of goitrogen-induced myxoedema due to *p*-aminosalicylate, the test result was only partially restored towards normal after one week's load. A repeated test, one month after another week of iodide load, showed restoration to normal (Table I). Evidently one week's KI load is not sufficient to restore such a severe iodide deficiency, and we have concluded that two weeks is the optimum period for a standard load.

Immediately after these iodide loads we can expect flooding with iodide, and consequent suppression of the radioiodine uptake (Keating and Albert, 1949; Childs, Keating, Rall, Williams, and Power, 1950). Previous observations of the rate of restoration of radioiodine uptake to normal after iodide medication have suggested the conclusion, which we have confirmed, that a lapse of one month

after an iodide load should suffice to rid the body of the excess of iodide (Keating, Haines, Power, and Williams, 1950). A longer lapse of time, if desired, should give equally valid results, but not a shorter one. It can, for example, be seen from Fig. 1 that a lapse of two weeks is insufficient for full elimination of the iodide-flooding effects; the tests at two weeks after the first two iodide loads did not show the full radioiodine avidity later revealed at 258 and 375 days.

TABLE I

Iodide-repletion Tests in a Patient with Goitrous Myxoedema after Treatment for Nine Months with p-Aminosalicylic Acid

		^{131}I *test-results*	
Test	*Days after stopping PAS*	*Urinary excretion 0–48 hrs. (% of dose)*	*'T' Index*
Initial	4	15·7	50·0
1 month after 1 week of KI load (10 mg./day) .	40	28·8	18·4
1 month after 2nd week of KI load (10 mg./day) .	80	47·7	14·5*

* Error in subdivision of urinary samples was suspected, and thyroid uptake probably normal (compare 0–48 hr. value).

Methods

A. *The iodide-repletion test.* (1) *Standard technique.* The patients reported here have all had a preliminary radioiodine test. On the decision to add this supplementary test, the patient is given 14 pills each containing 10 mg. of potassium iodide, and is instructed to take one daily for two weeks, and to report for re-testing with radioiodine four weeks after finishing the tablets. The radioiodine test used throughout this survey was the three-period urinary excretion test, from which is derived the *T* index of thyroid clearance (normal range 2·8 to 13) (Fraser, Hobson, Arnott, and Emery, 1953). (2) *Indications for this test.* The test, being designed to distinguish the avid thyroid uptake of iodine deficiency from that of thyrotoxicosis, is useful when (*a*) a simple radioiodine test has revealed an unexpectedly avid thyroid uptake of dubious clinical significance; for example, when the clinical picture either is merely one of a non-toxic goitre, or includes no more than minimal signs of hyperthyroidism; and when (*b*) an iodine deficiency is suspected, usually because of previous drugs; for example, after a prolonged course of antithyroid drugs. As such patients are not seriously ill, the delay involved does not hamper the clinical management; and it offers a useful period for assessing the patient's response to simple sedative treatment.

B. *The clinical survey of the iodide-repletion test.* For this survey we have used mainly the standard iodide-repletion test detailed above. We have also included the results obtained with two slightly modified procedures (differing only in that the iodide load had been given for either one week or one month), since they were largely equivalent. The figures showing the results (Figs. 2, 3, and 4)

indicate the duration of iodide load used for each test. Table II shows the clinical groups studied for this survey and the distribution of the standard and modified tests among them. All iodide-repletion tests performed at this hospital during the time of the survey are included, except for the five applied to patients shortly after radioiodine therapy. We have assessed the clinical validity of the

TABLE II

The Patients Surveyed

Grouping by diagnosis		*Number of patients subjected to iodide-repletion test 10 mg. KI given daily for*			
Initial	*Final*	*7 days*	*14 days (standard)*	*Other duration*	*Total*
A. Untreated ? thyrotoxicosis (also high thyroid uptake or exophthalmos)	1a. Severe thyrotoxicosis	0	0	0	0
	1b. Mild thyrotoxicosis (diagnosed at first visit)	9	5	0	14
	1c. Mild thyrotoxicosis (doubtful at first visit)	4	6	1	11
	2. Ophthalmic Graves' disease	1	2	0	3
	3. Anxiety state				
	(*a*) with non-toxic goitre	4	19	4	27
	(*b*) without non-toxic goitre	1	2	0	3
B. Untreated non-toxic goitre (also high thyroid uptake)	Non-toxic goitre	3	7	1	11
C. Euthyroid	1. No thyroid disease	1	2	0	3
	2. Non-toxic goitre	1	3	0	4
D. Previous antithyroid drug therapy	1. Clinical remission of thyrotoxicosis at follow-up	3	4	3	10
	2. Clinical relapse of thyrotoxicosis at follow-up	2	4	0	6
	3. Goitrogen myxoedema due to				
	(*a*) resorcinol	0	2	0	2
	(*b*) *p*-aminosalicylic acid	1	1	2	4
	(*c*) other drugs	0	1	0	1
					Total 99

test in three main groups of patients (Table II): (1) patients presenting clinically either a non-toxic goitre, or suspected but not clinically obvious thyrotoxicosis, in whom the simple radioiodine test showed an avid thyroid uptake; that is, the group showing avid thyroid uptake of dubious clinical significance; (2) patients with ophthalmic Graves' disease, that is, exophthalmos and nervousness, but no definite clinical signs of hyperthyroidism; and (3) patients who had just completed a prolonged course of antithyroid drugs (usually, but not always, for treatment of hyperthyroidism). As far as practicable, all patients coming into any of these categories during the period of the study were subjected to the test. We have also tested, as 'controls', some patients with initially normal results from radioiodine tests, and either no suspicion of thyroid disease or a non-toxic goitre. We have tested five patients at routine reassessment after ^{131}I therapy for thyrotoxicosis; but we have omitted them from this report, and

plan to present these findings in a separate paper when we have investigated more cases of this kind.

The results of the iodide-repletion tests have been evaluated against each patient's final clinical diagnosis—that is, the diagnosis made independently of these results, three months or more after the tests, in the light of the patient's clinical picture and response to therapy.

TABLE III

^{131}I Tests in a Patient with Goitrous Myxoedema due to Cobalt

Administration of cobaltous chloride was stopped 10 days previously.

Thyroid uptake measurements	*Measurement of secretion into plasma*
Urinary { *T* index of thyroid uptake = 35 (high); Total 0–48 hr. excretion = 7·5%	At 48 hours, plasma protein-bound ^{131}I = 0·9% of administered dose per litre of plasma†
Thyroid clearance (0–½ hr.) = 22% of extracellular fluid per ½ hr.*	
* Normal value = 1 to 10 per cent.	† Normal value < 0·5 per cent.

Results

1. *The need for the iodide-repletion test*

It might be thought that refinements of the simple radioiodine test procedure could supplant the need for this longer test. Table III shows the results of a full radioiodine test made on a patient who developed a goitrous myxoedema (basal metabolic rate, —19 per cent.; plasma protein-bound ^{127}I, 2·8 μg. per 100 ml.) after the administration of cobaltous chloride. It will be seen that not only the thyroid uptake, whether from neck measurements or urinary excretion indices, but also the plasma test (the appearance of plasma protein-bound radioactivity) indicate a rapid turnover of iodine by the thyroid. Similar results have been obtained in other such patients. Thus the plasma radioiodine measurement is not a reliable method for distinguishing severe iodine deficiency from thyrotoxicosis, though milder iodine deficiency may show a normal result with the plasma test along with an avid thyroid uptake, as found by Wayne (1954) in some of his patients with non-toxic goitres.

2. *Results of the clinical survey*

Figs. 2 to 4 show the initial and 'iodide-repletion' results of radioiodine tests for each patient. Each such pair of results is connected by a line indicating by its type the duration of the iodide load. Any radioiodine results suspected of erroneous urinary subdivision or collection are marked with an asterisk, and the 48-hour urinary excretion of ^{131}I recorded. The patients are grouped according to the mode of their initial clinical presentation (? thyrotoxicosis; ? non-toxic goitre; doubtful thyroid function after therapy), and sub-grouped by their final clinical diagnosis. Fig. 3 includes, for comparison, some results of tests in patients whose thyroid uptake was initially normal.

A. *Untreated patients with ? thyrotoxicosis*: that is, those suspected of thyrotoxicosis who also showed initially either exophthalmos or a high radioiodine uptake, or both (Fig. 2). (1) Among the 25 patients finally diagnosed as having mild thyrotoxicosis, all except one still showed an avid thyroid uptake when

re-tested after the administration of the iodide load. The exceptional patient showed minimal thyrotoxic features when tested, but has been placed in this group because four months later she developed new symptoms, with clinically obvious thyrotoxicosis. (2) Of the three patients with ophthalmic Graves'

FIGS. 2 to 4. A clinical survey of the iodide-repletion test.

Each vertical line represents one patient, and joins his or her initial test result (hollow circle) with the later test after iodide repletion (solid circle); the type of line indicates the duration of the iodide load (see key).

* Signifies that the ^{131}I test so marked is suspected of an error in urine collection; hence the footnote gives the U_{48} value of the test (the total percentage of ^{131}I excreted in the 48-hours urine).

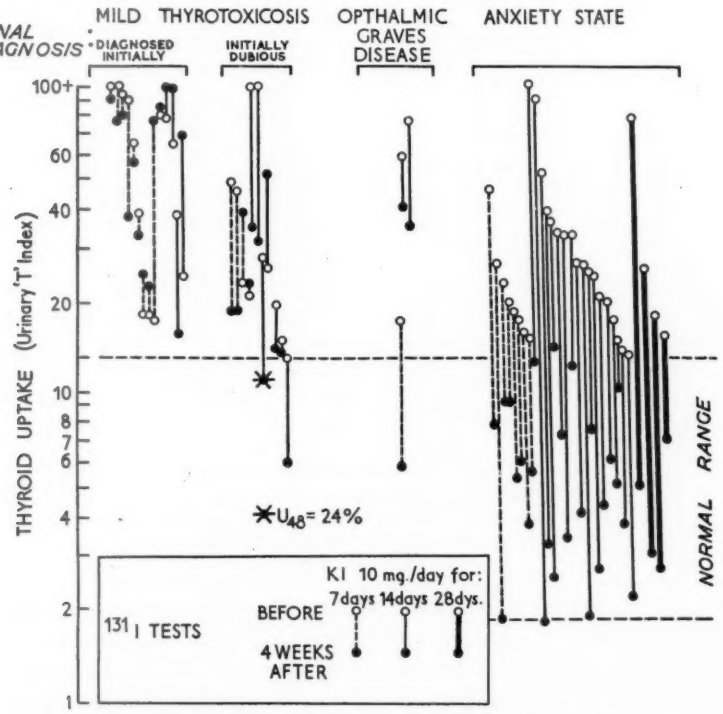

FIG. 2. Patients initially diagnosed as '? Thyrotoxicosis'.

It will be seen that the test has separated the patients in whom the final clinical diagnosis was thyrotoxicosis, with two exceptions.

disease, a group in which hyperthyroidism is by definition subclinical, two showed a persistently avid thyroid uptake; in one the thyroid uptake was restored to normal after the iodide load. (3) By contrast, 29 of the 30 patients finally diagnosed as suffering from anxiety states (26 with associated non-toxic goitres) showed normal tests after the iodide load. The exceptional patient gave an almost normal result in the final test, and was clinically normal when examined one year later.

B. *Untreated patients with a clinically non-toxic goitre showing avid thyroid*

uptake (Fig. 3). All these 11 patients showed a normal or low thyroid uptake after the iodide load.

C. *Euthyroid patients with initially normal thyroid uptake* (Fig. 3). After the iodide load these seven patients gave test results similar to those in the previous group.

D. *Patients tested after recent prolonged administration of antithyroid drugs* (Fig. 4). (1) *Treated thyrotoxicosis.* Of the 10 patients who, on later follow-up

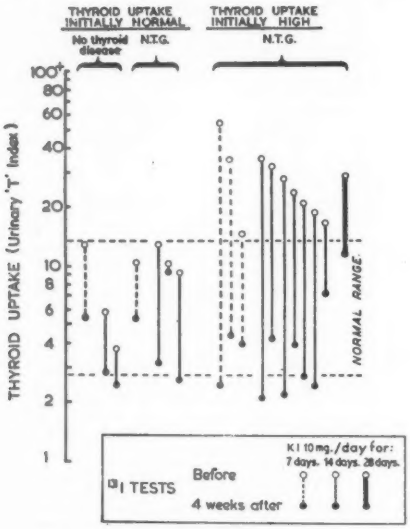

FIG. 3. Patients clinically euthyroid.
The results of iodide-repletion tests are all within the normal range, though several of the initial tests show an avid uptake.
N.T.G. = non-toxic goitre.

examination, were found to be in clinical remission, nine gave normal test results. The apparent exception arises from an error in the urine collection for the final test; in this case the total 48-hour urinary excretion was normal (64 per cent.). Of the six patients who later had a clinical relapse, all showed a persistently avid thyroid uptake after the iodide load. (2) *Goitrous myxoedema.* Seven patients were tested after the accidental administration of goitrogens (in most cases either resorcinol applied to varicose ulcers or *p*-aminosalicylic acid given for more than nine months in the treatment of tuberculosis). The result of the test was restored to normal after iodide loading in five cases, while in the two exceptions it was much nearer to normal figures.

Discussion

It is well recognized that high values for radioiodine uptake are found in a few patients without clinical evidence of thyrotoxicosis, especially in iodine-deficient districts (Stanbury, Brownell, Riggs, Perinetti, Itoiz, and del Castillo, 1954),

but also elsewhere, in a proportion of patients presenting clinically non-toxic goitres (Keating, Haines, Power, and Williams, 1950; Fraser, Hobson, Arnott, and Emery, 1953; Wayne, 1954), as well as in most patients at the conclusion of a period of antithyroid drug therapy (Keating, Haines, Power, and Williams, 1950). Outside iodine-deficient districts 5 to 20 per cent. of patients presenting clinically non-toxic goitres show an avid thyroid uptake. It is difficult to estimate this proportion because of the varying methods of selection used in the

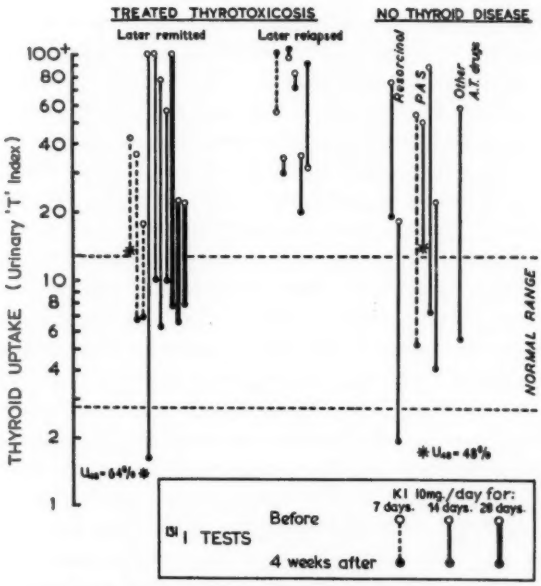

FIG. 4. Patients tested after prolonged administration of antithyroid drugs.

It will be seen that (1) among the treated thyrotoxic patients only those who later remained in remission gave normal results with the iodide-repletion test, and (2) among those found to have goitrous myxoedema due to antithyroid drugs, and consequent severe iodine deficiency, the results of the iodide-repletion test were normal in all but one, and nearly normal in the exceptional case.

different groups studied, and also because of the difficulty of excluding all patients with mild thyrotoxicosis, since in the earliest stages of this condition no clinical response to antithyroid drugs may be discernible. In the 'non-toxic goitre' groups cited below, some of the patients may have had subclinical thyrotoxicosis; but our results with the iodide-repletion test suggest that this would not apply to many of them, and that most of the avidity for radioiodine found in such patients is due to iodine deficiency. Fraser, Hobson, Arnott, and Emery (1953) found an avid thyroid uptake in 15 per cent. of 130 patients who were initially suspected of thyrotoxicosis, but finally diagnosed as suffering from non-toxic goitre because there was no clinical response to antithyroid drug

treatment, and in 8 per cent. of their 49 patients who initially presented clinically simple non-toxic goitres. Keating, Haines, Power, and Williams (1950) found that 20·4 per cent. of their patients with adenomatous goitre and without hyperthyroidism had a 48-hour urinary excretion of radioiodine outside the euthyroid range. Wayne (1954) found increased thyroid uptake in 10·5 per cent. of his 352 patients finally diagnosed clinically as having non-toxic goitres, though only 1·1 per cent. of them showed a rapid turnover by the plasma radioiodine test.

As would be expected, an avid radioiodine uptake is an early feature of experimental iodine deficiency; it was found in rats even when their deficiency of iodine had reached only 20 per cent. of the body's store and no goitre had yet developed; when their deficiency reached 40 per cent., the avidity reached its highest point, while no thyroid enlargement was recognized at a deficiency of less than an 80 per cent. (Catz, El Rawi, and Geiger, 1953). This avidity depends on stimulation of the thyroid, mainly indirectly, from excessive release of thyrotrophin from the anterior pituitary, but also to a lesser extent directly from the low iodide levels. Chapman (1941) has shown that some of this stimulation arises directly in the thyroid, since it occurs even in rats deprived of the hypophysis. In the iodine-deficient rat after hypophysectomy he found a 35 per cent. increase in the weight of the thyroid, and a 73 per cent. increase in thyroid cell-height, over the values found in rats on a normal diet after hypophysectomy. But neither of these indices of thyroid activity is raised to the level found in normal rats on a normal diet, so that the excessive avidity found in iodine deficiency must be mediated by pituitary stimulation of the thyroid. Leblond and Mann (1942) have adduced other evidence for the same conclusion; they found that the hyperplasia seen in the thyroids of rats fed on iodine-deficient diet was similar to that seen in the goitres induced by the administration of an antithyroid drug. Griesbach (1941) and Griesbach and Purves (1943) have shown from plasma assays, from pituitary histology, and from the effect of hypophysectomy, that the thyroid stimulation which follows administration of antithyroid drugs arises from excessive release of thyrotrophin from the anterior pituitary, which itself arises from defective secretion of thyroid hormone. Leblond and Mann (1942) also showed that the pituitary histology in simple iodine deficiency was identical with that found either after antithyroid drug administration or after thyroidectomy. It should therefore be possible to suppress the avid uptake of radioiodine in iodine deficiency, either by replacing the deficiency or by suppressing the excessive release of thyrotrophin from the anterior pituitary. Since this excess has evidently arisen from decreased thyroid hormone secretion induced by the iodine deficiency, the administration of normal or slightly supranormal amounts of thyroid hormone should achieve its suppression. This conclusion is in contrast with the finding, now established, that the avid radioiodine uptake of thyrotoxicosis is not suppressible, even down to the normal range, by the administration of normal or slightly supranormal amounts of thyroid hormone (see below). Hence we should have available two testing procedures, each of which can determine whether an

avid thyroid uptake of radioiodine is due to iodine deficiency or to thyrotoxicosis: the iodide-repletion test, and the thyroid hormone or tri-iodothyronine suppression test.

Our results with the iodide-repletion test suggest that most of the instances of high thyroid uptake found in patients without clinical thyrotoxicosis are at least partly dependent upon iodine deficiency; for we have found, on examining the patients from one to two years after the test, that there has been no development of clinical thyrotoxicosis or recurrence of the high thyroid uptake. Whatever its basis, the test has apparently distinguished these patients from those who have mild thyrotoxicosis and later show a recognizable clinical response to antithyroid therapy. This ability to differentiate the high thyroid uptake found in treatable thyrotoxicosis from that which is probably dependent on iodine deficiency is of great practical importance, especially when it is desired to assess thyroid function in patients who have just completed a course of prolonged antithyroid drugs; and we have found that the test results agree with the clinical outcome in such patients at follow-up examination. We do not yet know whether a similar agreement is achieved after radioiodine therapy.

Other radioiodine procedures have been suggested for distinguishing between thyrotoxicosis and cases of non-toxic goitre in which a high radioiodine uptake is probably due to iodine deficiency. Wayne (1954) has suggested that the plasma radioiodine test more often gives a normal result in these non-toxic goitres, which may be true as regards the lesser iodine deficiencies. But we have found that this test may also be 'falsely positive' with severe iodine deficiency, as would be expected theoretically. As already noted, the main alternative to the iodide-repletion test is the thyroid hormone suppression test, of which the most convenient clinical form is the tri-iodothyronine suppression test. It is now well established that the normal thyroid uptake of radioiodine can be suppressed by the administration of exogenous thyroid hormone, as desiccated thyroid (Greer, 1951), as thyroxine (Morgans, Oldham, and Trotter, 1951–2), or as tri-iodothyronine (Starr and Liebhold-Schueck, 1953) given either in daily dosage or by a single intravenous injection (Sharrer and Asper, 1956). The full suppressive effect is achieved at five to seven days in either case (Burrell, Higgins, and Fraser, 1956; McConahey and Owen, 1956; Sharrer and Asper, 1956); this interval corresponds to the lag-period found experimentally with the fall in thyroid uptake which follows hypophysectomy (Ghosh, Woodbury, and Sayers, 1951; Randall and Albert, 1951). The daily dosage required to achieve full suppression varies among normal subjects; for consistent suppression with tri-iodothyronine it must exceed 50 μg. per day, and is satisfactory at 140 to 180 μg. per day (McConahey and Owen, 1956; Higgins and Fraser, 1957); with desiccated thyroid three grains per day is effective only with some, and six grains per day with most subjects (Greer and Smith, 1954). These dosages, which are consistently suppressive with normal subjects, do not significantly depress the avid uptake of thyrotoxicosis (Werner, Hamilton, and Nemeth, 1952; Werner and Hamilton, 1953; Werner, 1956); and so their administration for seven days, followed by a radioiodine test, has been called the tri-iodothyro-

nine suppression test, advocated for confirming whether an unexpectedly high thyroid uptake really signifies thyrotoxicosis (Werner and Spooner, 1955; Perlmutter and Slater, 1955). As already mentioned, animal findings in experimental iodine deficiency suggest that the excessive uptake of the iodine-deficient thyroid arises from pituitary stimulation, and so should be suppressed in this test like the normal uptake. The findings reported up to date (Higgins and Fraser, 1957) suggest that the non-toxic goitres with high thyroid uptake behave similarly. On the other hand, failure to suppress in this test need not imply thyrotoxicosis. Whatever the initial uptake, this absence of suppression has been a feature of the thyroid uptake of ophthalmic Graves' disease (exophthalmos without clinical thyrotoxicosis), and also of that of the thyroid with an independently functioning adenoma which has not yet become toxic (Higgins and Fraser, 1957). Another minor disadvantage of this test is that it necessitates the administration of slightly supranormal amounts of thyroid hormone for about a week, in order that no normal uptake should escape suppression. This procedure may not be desirable in cardiac patients suspected of thyrotoxicosis; but such a confirmatory test is only needed in doubtful and therefore mildly ill patients.

Thus the available results suggest that the high thyroid uptake found with some non-toxic goitres may be distinguished from that found with thyrotoxicosis by either the iodide-repletion or the tri-iodothyronine suppression test. While the iodide-repletion test is simple and reliable, it involves a delay of six weeks; but it should then have corrected the basic iodine deficiency, which the quicker tri-iodothyronine test will leave uncorrected. Where a quick answer is needed, and the patient is not seriously ill, the tri-iodothyronine test may be preferred. When iodine is to be given to persons with hyperplastic thyroid glands, the development of an iodine-induced thyrotoxicosis, or *iod-Basedow*, such as Chesney, Clawson, and Webster (1928) found with their rabbits which were goitrous after antithyroid drugs, might be feared. But in about 200 such tests given to various patients with a high thyroid uptake we have not encountered this complication, nor even seen any exacerbation of thyrotoxicosis in the thyrotoxic patients tested. Stanbury, Brownell, Riggs, Perinetti, Itoiz, and del Castillo (1954) did see such a development in one iodine-deficient patient after he had been given 1·5 mg. of iodide per day for two to three months. But our procedure involves giving a higher iodide dosage for a shorter period; possibly this higher iodide dosage, which itself is in the therapeutically suppressive range (Childs, Keating, Rall, Williams, and Power, 1950; Stanley, 1949), thereby prevents any such development. Our clinical survey has included some instances of known iodine-deficiency, some patients suspected of mild but not obvious thyrotoxicosis, and some in whom the thyroid status needed assessment after antithyroid drugs, which had been given for some months, so that an iodine deficiency might be expected. The results of the iodide-repletion test correlated well with subsequent independent clinical assessment in all the circumstances in which the original simple radioiodine test was found to be misleading. This test should therefore be helpful in interpreting unexpectedly

high thyroid uptakes of doubtful clinical significance. It is particularly useful whenever a patient is to be tested with radioiodine after a prolonged course of antithyroid drugs.

One of the authors (C. D. Burrell) was in receipt of a grant from the Medical Research Council for part of this work. We gratefully acknowledge advice and assistance from Dr. J. E. S. Bradley, and assistance with the radioiodine measurements from Miss J. Biscoe and Mrs. M. Gray.

Summary

1. A standard iodide-repletion test is described for distinguishing iodine deficiency from mild thyrotoxicosis. For two weeks 10 mg. per day of potassium iodide are given, and the radioiodine test is performed four weeks later.

2. This test applied to untreated patients gave the following results: (1) Persistently avid uptake in 24 out of 25 cases of mild thyrotoxicosis. (2) Persistently avid uptake in two out of three cases of ophthalmic Graves' disease. (3) Normal uptake in 29 out of 30 patients with anxiety states (27 with non-toxic goitres) in whom thyroid uptake was initially high. (4) Normal or low uptake in all 11 patients with non-toxic goitre who showed an initially high thyroid uptake, and also in the other euthyroid patients tested.

3. The test applied after previous prolonged administration of antithyroid drugs showed: (1) Persistent avidity in all of six treated thyrotoxic patients who later relapsed. (2) Normal uptake in nine out of 10 treated thyrotoxic patients who later remained in remission. (3) Normal uptake in five out of seven patients with goitrous myxoedema due to antithyroid drugs given for other reasons, and a value very much nearer normal in the other two.

4. The iodide-repletion test is recommended when the simple radioiodine test reveals an unexpectedly avid thyroid uptake of dubious clinical significance, and also for testing patients who have been receiving antithyroid drugs.

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THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1957

FIFTY-FIRST ANNUAL GENERAL MEETING

THE FIFTY-FIRST ANNUAL GENERAL MEETING was held in Edinburgh at the Assembly Rooms, George Street, on Friday and Saturday, May 17 and 18. The attendance-book was signed by 239 members and 33 visitors.

The President, Sir Russell Brain, Bt., was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read, confirmed, and signed. The following Officers, Executive Committee, and Honorary, Overseas Honorary, Senior, and Ordinary Members were elected unanimously:

Executive Committee

President:	Professor Sir L. S. P. Davidson.
President-Elect:	Dr. J. R. H. Towers.
Treasurer:	Dr. C. Newman.
Secretary:	Dr. C. M. Fletcher.
Members for England and Wales:	Dr. E. E. Pochin.
	Professor H. Scarborough.
	Dr. W. Brockbank.
	Dr. J. S. Richardson.
	Dr. D. V. Hubble.
	Dr. K. Robson.
Members for Scotland:	Dr. A. A. F. Peel.
	Dr. I. Gordon.
	Professor D. M. Dunlop.
Members for Ireland:	Dr. L. K. Malley.
	Dr. Brendan O'Brien.
	Dr. J. T. Lewis.

Election of Honorary Member
Sir W. Russell Brain, Bt.

Election of Overseas Honorary Member
Sir Charles Bickerton Blackburn.

Election of Senior Members

Present Honorary Members

Dr. Hugh Barber.	Dr. F. G. Hobson.
Dr. J. Murray Bligh.	Professor Sir William Hume.
Sir Harold Boldero.	Dr. C. G. Imrie.
Dr. J. M. H. Campbell.	Dr. F. G. Lescher.
Professor Sir David Campbell.	Dr. Robert Marshall.
Dr. S. B. Boyd Campbell.	Professor J. C. Meakins.
Dr. R. C. Clarke.	Professor A. E. Naish.
Professor Philip C. P. Cloake.	Dr. P. T. J. O'Farrell.
Sir John Conybeare.	Professor T. H. Oliver.
Dr. J. N. Cruickshank.	Dr. S. W. Patterson.
Professor Sir Neil Hamilton Fairley.	Sir Alun Rowlands.
Sir Francis Fraser.	Dr. David Smith.
Dr. George Graham.	Professor A. P. Thomson.
Dr. T. L. Hardy.	Dr. G. E. S. Ward.

Former Members

Sir J. Charlton Briscoe.
Dr. E. T. Freeman.
Dr. A. Fergus Hewat.
Dr. Ivy McKenzie.
Dr. Douglas McAlpine.
Professor Charles McNeil.
Professor Adam Patrick.
Professor Sir Rudolph Peters.

Ordinary Members

Dr. Robert Coope.
Professor J. M. O'Donovan.
Dr. Donald Paterson.
Dr. J. K. Rennie.
Sir Charles Symonds.
Dr. F. H. Young.

Election of Ordinary Members

Philip Derek Bedford, M.D., M.R.C.P., Consultant Physician, Cowley Road Hospital, Oxford.

Helen Dimsdale, M.D., F.R.C.P., Neurologist, Royal Free Hospital.

John Rogers Ellis, M.D., F.R.C.P., Assistant Physician, London Hospital.

George Roche Fearnley, M.D., M.R.C.P., Consultant Physician, Gloucestershire Royal Hospital.

Edward Brodie French, M.B., M.R.C.P., Senior Lecturer in Medicine, University of Edinburgh.

George Stanley Graveson, M.D., M.R.C.P., Area Neurologist, Western Area.

Philip Hugh-Jones, M.D., M.R.C.P., Lecturer in Medicine, Postgraduate Medical School of London.

John Gordon MacArthur, M.B., M.R.C.P., Senior Lecturer in Therapeutics, University of Glasgow.

John George Macleod, M.B., F.R.C.P.E., Lecturer in Medicine, University of Edinburgh.

Risteard Mulcahy, M.D., M.R.C.P., Assistant Physician, St. Vincent's Hospital, Dublin.

Kenneth Palmer, M.D., M.R.C.P., Senior Lecturer in Medicine, University of Aberdeen.

John Lawrence Pinniger, D.M., M.R.C.P., Physician in Clinical Laboratories, St. Thomas's Hospital.

Alfred George Spencer, M.D., M.R.C.P., Senior Lecturer in Medicine, University College Hospital.

Arthur John Thomas, M.D., M.R.C.P., Consultant Physician, United Cardiff Hospitals.

Owen Lyndon Wade, M.D., M.R.C.P., Professor of Therapeutics and Pharmacology, Queen's University of Belfast.

The Secretary explained that the Senior Members nominated by the Committee were in three classes: former Honorary Members who had not been Past Presidents or Original Members, former Members who had resigned under Rule 2 and who on receipt of a circular letter had expressed a desire to be so nominated, and Ordinary Members retiring this year who by their regular recent attendance had shown an active interest in the Association.

The Treasurer, in presenting his accounts, pointed out that the margin between receipts and expenses was narrowing each year, and now was only £128. This was due chiefly to the increasing cost of the journal, the cost of which to members had been raised from 30*s*. to 35*s*. per annum. It was possible that the Editors would have to ask the Executive Committee to consider raising the subscription to cover this. The Treasurer, seconded by Dr. A. M. Cooke, proposed the adoption of the accounts and the provision of a donation of £300 from the Association's reserves, to enable extra pages to be printed in the ensuing year's journal.

Date of Meeting at Leeds in 1958. The Secretary said there was a choice of two dates. The Cardiac Society were to meet in Leeds on April 17 and 18. They had proposed last year that owing to their full programme they should extend their meeting on to the Friday morning, and had asked that there should be a joint meeting with the Association. This proposal had been rejected. The Leeds members now suggested that if the Association were to meet on April 18 and 19 the Cardiac Society could be accommodated separately on the Friday morning. The alternative was for the Association to meet, as was their usual custom, at Whitsun (May 23 and 24). Professor A. A. Moncrieff said it would be convenient if the Association would stick to Whitsun for its meetings, so that other Societies wishing to avoid a clash could arrange their meetings well in advance. Dr. J. R. H. Towers, speaking for the Leeds members, said that either date would suit them. On putting the alternative dates to the vote there was a large majority in favour of meeting at Whitsun in 1958.

Place of Meeting, 1959. Professor H. Scarborough's invitation to the Association to meet in Cardiff in 1959 was accepted.

The newly elected President, Sir Stanley Davidson, then took the Chair, and thanked

Sir Russell Brain for his conduct of the Association's business and his account of its history in its Jubilee year.

SCIENTIFIC BUSINESS

Friday Morning, May 17

1. Dr. Douglas Guthrie (introduced) suggested that, as a preface to a meeting which was to deal with medicine of the present and of the future, it might be appropriate and helpful to glance at the past, and to review briefly the *Early Days of Medical Education in Edinburgh*. The possession of a degree or diploma did not become the essential passport to the practice of medicine until 1858, barely a century ago, although much had happened before that date. The University of Edinburgh, or Town's College, the youngest of the four Scottish universities, was founded in 1583, not by the Church, like its three sisters, but by the City, as its original name implied. Only a few M.D. degrees had been awarded before the Faculty of Medicine was founded, in 1726, by Alexander Monro, primus, and four of his associates, Rutherford, Plummer, St. Clair, and Innes, who had been his fellow students at Leyden University, when Hermann Boerhaave was widely renowned as a teacher and physician. The new Edinburgh Faculty was loyally supported by the Surgeons, whose 'Incorporation' had received Royal assent as early as 1505, and by the Physicians, whose Royal College had been founded in 1681 by Sir Robert Sibbald, another Leyden student, and by Archibald Pitcairne, the youngest original Fellow, who was appointed Professor of Medicine at Leyden in 1692 where, it was said, Boerhaave was one of his students. Botany and chemistry had been taught in the University, and anatomy in the College of Surgeons, for many years before the Faculty was established, while clinical training was acquired by the prevailing system of apprenticeship, which at least had the merit of teaching much that could not be learned from books or lectures.

Dr. Guthrie referred to the establishment of a Chair of Surgery in 1831, the subject having been taught along with anatomy before that time, just as materia medica had been regarded as an adjunct of botany. The first Professor of Pathology was John Thomson, who had previously held the Chair of Surgery in the College of Surgeons, and subsequently that of Military Surgery in the University. He was an able and versatile figure in the Edinburgh School of that day. Reference was also made to the achievements of the great eighteenth-century physicians, Robert Whytt, John Gregory, and William Cullen, and of later teachers such as James Syme, James Young Simpson, and Joseph Lister, whose contributions had added so vastly to knowledge.

Dr. Guthrie illustrated his remarks by an interesting series of lantern slides, and concluded that as we reviewed the work of those pioneers we ought to visualize the difficulties they encountered, unknown and forgotten in our modern environment. It was also salutary to attempt to recapture for ourselves some of the curiosity, the enthusiasm, and the deep human insight which dominated the lives of many of the physicians who maintained at so high a level the standard of medical education at Edinburgh in the early days.

2. Drs. J. Reid, A. I. MacDougall, and M. M. Andrews (introduced) said that disappearance of glycosuria and the return of the fasting blood-sugar to normal in a diabetic receiving full salicylate treatment for acute rheumatism had led to reinvestigation of the *Effect of Aspirin in Diabetes Mellitus*. A short intensive course of aspirin controlled by serum-salicylate estimations had been given for 10 to 14 days to another seven diabetics, and the effect on the clinical manifestations and on biochemical abnormalities had been investigated. The patients had been given a constant low-carbohydrate diet throughout the investigation, which had been started for two weeks before the course of aspirin to assess the effect of diet alone. Aspirin had led to a progressive fall in fasting blood-sugar level in every patient, so that by the end of the course of treatment the fasting blood-sugar concentration had been normal or near normal. It had also led to disappearance of glycosuria, and had reduced ketonuria to normal in two patients. In five patients the blood-sugar curve during aspirin therapy was much lower than it had been before, or after the drug was discontinued. These results had been achieved without loss of weight in any of the patients during the period of giving aspirin, except in one overweight mild diabetic.

Characteristic symptoms of the disease, such as thirst, polyuria, and pruritus, had disappeared as fasting blood-sugar levels fell and glycosuria cleared, and these symptoms had tended to be replaced by minor but nevertheless annoying side-effects from salycilate, principally tinnitus and slight deafness. Two patients who had rapidly developed very high serum-salicylate levels had suffered more severe toxic effects, persistent nausea going on to vomiting in one of the patients, but these symptoms had been quickly controlled by reducing the dose of aspirin.

Professor R. B. Hunter said that a considerable amount of work had already been done on the effect of salicylates in lowering the blood-sugar in animals and *in vitro*, in an

attempt to elucidate the effect on the glycolytic cycle, particularly by the research group in King's College; he would therefore ask Dr. Reid whether he had done any blood electrolyte or pH studies. It would appear from published work that the mode of action of salicylates in reducing hyperglycaemia in diabetic patients was a peripheral one, but the exact mechanism was as yet unknown.

Dr. J. D. Nabarro asked how the present findings could be reconciled with previous reports of hyperglycaemia and glycosuria during prolonged high dosage with aspirin.

Dr. K. Robson asked whether PAS, in the usual dosage for antituberculous therapy, had any effect on the blood-sugar.

Dr. Ian Murray asked whether any failures with aspirin in lowering blood-sugar levels had been encountered, since the action of aspirin had been likened to that of the sulphonylureas, substances whose action had been found unpredictable. He also pointed out that the young diabetic patient had been maintained on an exceptionally low carbohydrate intake during the period of the trial with aspirin, and inquired whether the reappearance of glycosuria at its termination coincided with resumption of a more normal diet.

Professor Robert Platt inquired about the effect of aspirin on the blood-sugar of the non-diabetic.

Dr. C. Hardwick asked if he was right in drawing the conclusion that aspirin had no effect on the diabetic state of these patients, as shown by the glucose tolerance tests, but that it merely depressed the fasting blood-sugar.

Dr. A. I. MacDougall (introduced) said, in reply to Dr. Nabarro and Professor Platt, that the patients in whom hyperglycaemia and glycosuria were observed during aspirin administration were under treatment for rheumatic fever and were not diabetic; preliminary observations in other non-diabetic subjects supported the view that the effect of aspirin on carbohydrate metabolism in these subjects differed from its effect in diabetics. In reply to Dr. Robson he mentioned a report in the French literature (Langeron *et al.*, *Presse méd.* **58**, 1037, 1950), that PAS had a hypoglycaemic action in tuberculous diabetics.

In reply to Professor Hunter, Dr. Reid said that their main concern had been to establish the clinical and biochemical action of aspirin in diabetes. They had shown that salicylate raised plasma pH and lowered plasma CO_2, but did not know if this held in diabetes. With regard to Dr. Ian Murray's questions, consecutive patients had been studied without failure to lower the blood-sugar levels. The young patient had been given the low-carbohydrate diet to show the need for additional therapy, and it had been maintained for the whole period. He assured Dr. Hardwick that blood-sugar curves during aspirin therapy had always been lower than they had been before or afterwards. During the course of aspirin therapy the curve became more and more normal, which implied that aspirin improved oral glucose tolerance, but further investigations were necessary.

3. Dr. J. Crooks, Dr. I. P. C. Murray (introduced), and Professor E. J. Wayne described *A Clinical Method of Assessing the Severity of Thyrotoxicosis*. A number of symptoms and signs of thyrotoxicosis had had numerical values allocated to them from a statistical discriminant analysis of the frequency of their presence or absence in cases of thyrotoxicosis and normal subjects. A film was shown to illustrate identification of the symptom of hyperkinesis, which had a high numerical value. The method had been applied to 300 subjects, of whom 182 had been unequivocally toxic or non-toxic and 118 had presented diagnostic difficulty. The scores or diagnostic indexes produced complete separation between toxic and non-toxic in the first group, and good separation in the doubtful group. Observer-error studies were described, showing that no statistically significant difference existed between the scores obtained independently by experienced observers. The method had been applied in four different centres to 171 patients referred for thyroid investigation, and the diagnostic accuracy had been comparable with that of the present series. This order of accuracy (85 per cent.) compared favourably with that obtained by radioiodine studies. That the score could be used to assess severity of toxicity was shown by the significant correlation between score and both four-hour uptake of radioiodine and basal metabolic rate. A therapeutic index had been derived from the diagnostic index by eliminating those features unchanged by antithyroid drug therapy. The changes in therapeutic indexes of 20 patients receiving methyl thiouracil were shown to follow closely the changes in the basal metabolic rates. The authors concluded that this quantitative method of expressing clinical evidence was useful in diagnosis, in assessing severity, and in evaluating therapeutic responses.

Professor G. W. Pickering remarked that he had wondered for a long time what was wrong with him. Professor Wayne's film made him realize that it was really thyrotoxicosis. He would like to ask two questions. First, how did the authors know how many marks to assign to each characteristic? Had they tested them out on a statistical basis? In his

experience he would have thought that in this country loss of weight and increased appetite counted for more than intolerance to heat. Secondly, it seemed there was a significant correlation between basal metabolic rate and clinical 'points' throughout the whole series. Was it not possible that there was a continuous series including both supposed normality and thyrotoxicosis?

Dr. J. H. Wright was not impressed by the cinematic demonstration of hyperkinesis, while the normal control seemed to him to be abnormally placid and deliberate in her actions. He doubted if it was possible to carry out full medical investigation without the use of leading questions. If the patients had been sent to a special thyroid clinic, it was highly probable that they had already been diagnosed as possibly thyrotoxic. If the trained observers taking part in the test were all members of one unit, they would be influenced in their assessments by training under the head of the unit.

Dr. Douglas Hubble said that he had used the diagnostic index in his out-patient clinic for the previous three months and had found it a stimulating and useful exercise. Those who disliked the mathematical approach to symptomatology should remember that the diagnosis of thyrotoxicosis might be difficult—not for themselves, of course, but for their less astute colleagues. The value of this numerical approach was shown by an examination of the articles on thyrotoxicosis in textbooks of medicine. Osler's famous textbook in its older editions, for example, did not mention hyperkinesis or intolerance of heat, nor loss of weight or the presence of an enhanced appetite. Some British textbooks, however, would obtain a high score in the diagnosis of thyrotoxicosis by the diagnostic index.

Dr. D. K. O'Donovan had tried this diagnostic method during the past month with some success, although there were a few weaknesses. With inexperienced workers there might be difficulty in assessing the value of some signs which were dependent on their rate of development rather than on their presence or absence, such as sensitivity to heat and cold. Other signs which were relatively pathognomonic were not given sufficient weight, for example, recent exophthalmos. The therapeutic criteria were unsatisfactory, since patients with a pure anxiety state gained considerable weight after thyroidectomy without clear evidence of previous hyperthyroidism.

Professor Russell Fraser said that he was sure the Association would welcome an emphasis on clinical methods, but wondered whether the suggested method did more than index the degree of clinical obviousness of the thyrotoxicosis.

Dr. A. G. MacGregor said that he had had the opportunity of using the diagnostic index for patients attending a busy endocrine clinic, and had found that it provided a useful guide to the clinical severity of thyrotoxicosis. He felt, however, that the weighting applied to the scores for some symptoms and signs, in particular hyperkinesia, might be reviewed; but he welcomed the attempt to give a quantitative value to clinical impressions.

Dr. P. Levine (introduced) emphasized the word 'severity' in the title of the paper, which might have various interpretations. For instance, cases with cardiological complications appeared to present special features, such as premature greying of the hair. He was uncertain of the general applicability of the proposed diagnostic scheme.

In reply, Dr. Crooks emphasized that the scores had a statistical basis. They had been provisionally allocated on the basis of a symptom analysis previously carried out by Professor Wayne, and had been modified to minimize observer-error effects and to produce the maximum separation between toxic and non-toxic subjects. There was a significant correlation between the basal metabolic rate and the indexes when toxic and non-toxic groups were considered together. It was possible, therefore, that a continuous spectrum of hyperthyroidism did exist, but further study of this concept was desirable. He admitted that the recognition of hyperkinesis was difficult, but, because of its particular diagnostic value in patients without a goitre or eye signs, as in the case of the patient shown in the film, it was diagnostically rewarding. Leading questions could be avoided. All the patients in the doubtful group had already been provisionally diagnosed as possibly thyrotoxic. In fact, 57 per cent. of these patients were shown to be non-thyrotoxic, and the value of the index lay in more confident exclusion of these difficult cases. The objection to the factor of common training, pointed out by Dr. Wright, had been met by the design of the observer-error studies and by the results reported from other centres. The therapeutic index was used only in unequivocally toxic cases, so that the situation envisaged by Dr. O'Donovan would not arise. It was clear from Dr. Levine's observations that individual clinicians placed special significance on various features. Such individual preferences had no statistical basis, and were responsible for the variability of subjective conclusions, whose avoidance had been one of the objectives of the study.

4. Dr. R. W. Luxton, discussing *Some Observations on Hashimoto's Disease*, illustrated the typical clinical picture of the middle-aged woman with hypothyroidism and a firm goitre, and described variants. Hashimoto's disease might appear clinically as Graves'

disease or as primary myxoedema without goitre. Following the observation of hepatomegaly and splenomegaly in Hashimoto's disease, tests of liver function had been started as a routine in 1952, and 39 cases had been studied. Of 16 untreated patients, the results had been abnormal in 14. Previous treatment by surgery, radiotherapy, and especially by dried thyroid gland, modified the results of the flocculation tests. Conclusions reached jointly with Dr. R. T. Cooke, who had made similar observations independently, were, first: that in untreated Hashimoto's disease the serum flocculation tests were positive sufficiently often to make them of diagnostic value. The colloidal gold test was usually more sensitive than the thymol turbidity, but both tests were necessary; secondly: that the best treatment of typical cases of Hashimoto's disease was dried thyroid gland by mouth. The serum flocculation tests depended upon an increase in gamma-globulin, and were non-specific. The tests were useful in the differential diagnosis of the nature of a goitre, for of 66 other goitrous patients only one had given abnormal test results. In 11 patients with proved malignant goitres, the serum flocculation tests had been negative. Both the serum precipitin test and serum flocculation tests were necessary for diagnosis, since either test might be negative when the other was positive. The observation of a nephropathy in Hashimoto's disease, probably glomerulonephritis, and the curious partnership between Hashimoto's disease and Paget's disease of bone, were mentioned. Of 35 patients with Hashimoto's disease, three had shown clinical Paget's disease, and a limited radiological bone survey had shown that seven of the 35 had Paget's disease. This difference was statistically highly significant.

Dr. D. V. Hubble said that seven new cases of Hashimoto's disease had been diagnosed in Derby in the previous seven months. Of these seven, five had shown positive flocculation tests; two had had hypergammaglobulinaemia; seven had shown positive precipitin tests to thyroglobulin (one had been negative in the laboratory of the Derbyshire Royal Infirmary, but Dr. Doniach had obtained a weak positive reaction); in three out of four patients Trotter's perchlorate ^{131}I test had been positive, and in one negative. In five of the seven patients the diagnosis had been confirmed by histological examination. Four of the patients had been hypothyroid, and three euthyroid. Dr. Luxton and Dr. Cooke were to be congratulated on having struck a trail which had already taken us a long way and was certain to take us further. As far as he knew, this disease was the first example of an immune reaction to a normally occurring endogenous substance—thyroglobulin.

5. Dr. Evan Bedford and Mr. Holmes Sellors (introduced) described their experience of the *Surgical Treatment of Atrial Septal Defects* at the Middlesex Hospital. They had used open heart surgery, under hypothermia induced by surface cooling to a temperature of 30° C. The main anatomical forms of defect were (1) atrio-ventricular (ostium primum), (2) fossa ovalis (ostium secundum), and (3) superior caval. These could usually be identified before operation. They had confined surgery to fossa ovalis defects, excluding all atrio-ventricular defects, and they had so far postponed operating on superior caval defects complicated by anomalous pulmonary veins. In closing low defects astride the inferior caval orifice, it was easy to deflect the inferior caval blood into the left atrium, as had happened in three cases, and this required surgical correction, which had been successful in two. They regarded obstructive pulmonary hypertension with high vascular resistance, systemic hypertension, and advanced age as contra-indications to surgery. Associated mitral stenosis had been relieved by valvotomy in three cases, and pulmonary stenosis once. They had operated on 40 patients aged between six and 55 years; seven of them were over 40, and five had had heart failure before operation. There had been only one fatality, which had resulted from a second operation to restore the inferior venacaval stream into the right atrium. Closure of an atrial septal defect in patients over 40 with grossly enlarged hearts was often beneficial, but the aim of surgery should be to restore normal function while the heart and pulmonary vessels were still intact, namely before the age of 20.

Professor J. McMichael pointed out that operation was not always to be advised. Some subjects with atrial septal defects survived undisabled to a ripe old age. He had seen the diagnosis made incidentally in four patients over the age of 55, and in one aged 72 *post mortem*. A similar series had been reported from Liverpool.

Dr. W. Evans congratulated Dr. Bedford and his team on their remarkable success, since the surgical closure of atrial septal defects would always remain a risky procedure. The hazard had to be weighed against the benefit. Many patients without excessive pulmonary blood-flow survived 60 years. The main difficulty was to recognize associated pulmonary hypertension, for the electrocardiogram was abnormal in uncomplicated atrial septal defect. If pulmonary hypertension was present it indicated irreversible obstructive changes in the lesser pulmonary arteries, and in these cases the operation would produce no lasting benefit. Patients suitable for operation were young, with considerable pulmonary blood-flow and without pulmonary hypertension.

DR. A. A. F. PEEL asked whether the use of intracoronary neostigmine obviated the necessity for blood pH estimation immediately before occlusion of the circulation. He also asked whether there was any certain method of differentiating septum-secundum and septum-primum defects before operation.

DR. B. E. SCHLESINGER said that in his experience atrial septal defects could carry the most serious prognosis of all congenital heart malformations in young children. For this reason they might never reach the cardiac clinics of the previous speakers, who might therefore have obtained a biased view of the ultimate outcome. He had found that surgical intervention was the only hope for young children and infants with grave complications from this defect such as cardiac failure and anginal attacks.

DR. MAURICE CAMPBELL had found that patients who survived the hazards of the first year or two nearly all did well for two or three decades, although they already had very large hearts. He thought that 85 per cent. of them were well by the time they reached 30 years, but that after this the prognosis became much worse, although a few continued to do well more or less indefinitely; some developed right-sided congestive failure without any rise of pulmonary arterial pressure, but in others this pressure rose so that the left-to-right shunt was reversed and they became cyanotic, with a risk of pulmonary thrombosis. He pointed out that this natural course of the disease meant that the average child could afford to wait until surgical closure could be carried out with relatively little risk.

In reply, DR. BEDFORD agreed that atrial septal defect was occasionally encountered in patients aged 50 to 65, but these represented only a small minority of any large series of cases, and they had found gross cardiac enlargement in 60 per cent. of patients over the age of 40. They had not encountered children as young as those whom Dr. Schlesinger saw, and their experience corresponded to that of Dr. Maurice Campbell. They agreed entirely with Dr. William Evans that serious pulmonary vascular disease occurred in about 15 per cent. of cases, and they regarded it as a contra-indication to closure of the septal defect. They had not encountered any serious acidosis during hypothermia by the method they employed, and they no longer estimated the pH of the blood during operation. Neostigmine was used as a routine in all cases.

6. DRS. A. K. SINHA, MAX ZOOB, S. M. RAB (introduced), and J. F. GOODWIN had studied 21 cases of *Organic Rheumatic Tricuspid Valve Disease*. Thirteen cases had been observed clinically; the diagnosis had been confirmed by haemodynamic studies in seven, and by autopsy in eight. A further eight cases had been studied retrospectively, by examining the autopsy and case records of 200 consecutive cases of rheumatic heart disease which had come to autopsy in the past 10 years. All the patients had had associated mitral valve disease and 11 had also had aortic valve disease. Fifteen had been female and six male. Contrary to expectation, the presence of tricuspid stenosis had not entirely prevented pulmonary congestive symptoms; for dyspnoea on effort had always been present, and paroxysmal dyspnoea and pulmonary oedema had been present in six cases. By contrast, only four patients had had ascites. The history had therefore not been of great value in diagnosis. In the absence of pulmonary hypertension or of atrial fibrillation, the diagnosis could be made from a giant presystolic 'a' wave in the jugular vein, a long PR interval, hepatic enlargement, and right atrial without right ventricular enlargement, as shown by X-rays. A tricuspid diastolic murmur at the lower end of the sternum was additional evidence. Pulmonary hypertension made the diagnosis more difficult, but it should be suggested if right atrial enlargement and the height of the 'a' waves were disproportionate to the pulmonary hypertension. With atrial fibrillation there was always a systolic wave in the jugular vein, and the diagnosis was between organic tricuspid insufficiency with stenosis and tricuspid insufficiency secondary to mitral valve disease.

DR. A. HOLLMAN (introduced) had found that the rheumatic tricuspid valve usually appeared to be incompetent when seen *post mortem*. Even when the valve was tightly stenotic there seemed to be incompetence in over half the specimens. He asked whether Dr. Goodwin's clinical observations agreed with this observation.

DR. GOODWIN replied that systolic pulsation in the jugular venous pulse suggested incompetence of the stenotic tricuspid valves in all but one of the cases with atrial fibrillation. One of the patients, who had previously had a large 'a' wave, developed systolic pulsation with the onset of fibrillation; there was a tricuspid systolic murmur in five of the six cases with a diastolic murmur, and the pathological anatomy of the valves also suggested incompetence.

7. DR. C. B. MCKERROW and MRS. M. MCDERMOTT (introduced by DR. J. C. GILSON) described *Short Term Respiratory Changes in Cotton Mill Workers*. The investigation had been designed to study the physiological effects of byssinosis, particularly the way in which the ventilatory capacity of cardroom workers changed throughout the day during the working week. The indirect maximum breathing capacity (M.B.C.) and the airways

resistance (A.W.R.), by the interruptor technique, had been measured at intervals spanning each working day from Monday to Thursday in a group of 12 subjects with clinical symptoms of byssinosis. It was found that a steady fall in M.B.C. and a rise in A.W.R. occurred each day. In the subjects with grade 1 byssinosis these changes decreased as the week progressed, while in grade 2 they remained fairly constant. A group of 12 workers from the same mill without clinical byssinosis showed similar daily changes, but of much smaller magnitude. In a further experiment eight of the byssinotic subjects had been removed from the mill for one Monday, when the fall in ventilatory capacity and rise in airways resistance had not occurred. A group of 33 colliers had been studied before and after their work. In contrast with the cotton workers, these men had shown a small rise in M.B.C. and fall in A.W.R. Since the dust concentration in the mine had been at least as great as in the cotton mill, it was concluded that the physiological changes seen in byssinotics were probably related to an active constituent of cotton dust, rather than to fatigue or a non-specific dust effect.

Professor Melville Arnott asked whether antispasmodics or the use of protective masks had any effect on the respiratory impairment, and also whether there was any relation between byssinosis and metal fume fever.

Dr. C. M. Fletcher said that the reaction to dust was quite unlike an allergic response, and wondered whether it could be attributed to the gradual exhaustion of some protective substance which was regenerated during the week-end. He asked also whether the apparent decline in M.B.C. before starting work, throughout the week, was significant.

In reply, Dr. McKerrow said that adrenaline aerosol reversed the physiological changes almost completely, but 25 mg. of phenergan did not protect. There had been no controlled trial of the effect of masks, although many of the workers considered the simple Martindale mask to be helpful. So far as was known there was no relation between byssinosis and metal fume fever. The lower initial M.B.C. readings on Tuesday to Thursday compared with Monday suggested that the effect of the dust was not entirely eliminated during the night, but these differences were not statistically significant. The fall during the day could be related to the exhaustion of some protective substance, or could equally well be due to the slow release of an active substance from the inhaled dust.

During Friday afternoon there were over 50 clinical and scientific demonstrations at the Royal Infirmary by members of the staff of the pre-clinical and clinical departments of the University of Edinburgh, and by the staff of the Royal Infirmary. Tea was provided in the Florence Nightingale Home through the courtesy of the Board of Management.

Annual Dinner

The Annual Dinner was held in the Upper Library of the University in the Old Quadrangle, the Edinburgh members kindly providing sherry beforehand. Before dinner the Pipes and Drums of the Edinburgh University Officers' Training Corps played in the quadrangle. The President, Professor Sir Stanley Davidson, was in the Chair. The toast of the Association was proposed by the President, and that of the guests by Professor Stanley Alstead. Sir Edward Appleton, the Principal and Vice-Chancellor of the University, replied, and the toast of the President was proposed by Professor D. M. Dunlop. During dinner the castle was floodlit.

Saturday, 9.15 a.m.

8. Dr. E. G. L. Bywaters and Dr. G. T. Thomas (introduced) discussed the *Prevention of Beta-Haemolytic Streptococcal Infection and Recurrences in Children with Rheumatic Fever*. Since streptococcal infection was an essential part of rheumatic fever and of its recurrences, there was a good theoretical basis for prophylactic treatment by sulphonamides or penicillin. Since prophylaxis had been introduced in 1939 it had been widely used in the U.S.A., but was still very little used in this country, perhaps because recurrences seemed to be less frequent here than in the States. Nevertheless, the importance of recurrences of rheumatic fever in producing cardiac damage was illustrated by 134 patients who had been observed for periods over five years without any chemoprophylaxis. Of 74 patients without any significant abnormality of the heart at follow-up, only seven had had more than one attack, whereas in the remaining 60 patients with loud murmurs and often cardiac enlargement, 34 had had two or more attacks. Eighty-nine of these patients had been clinically comparable to another 84 who had been given 1 gm. of sulphonamide daily during and after hospital admission. The total mean recurrence rate over a period of five years was 5·2 per cent. in the unprotected group and 1·4 per cent. in the protected group. In two of the five recurrences in the protected group it was found that the patients had not been taking the tablets. Difficulties encountered in administering prophylaxis arose

from parental apathy, and from lack of appreciation of its value by doctors and their fear of toxic reaction and hypochondriasis. All the toxic reactions in the series had occurred in the first three months, and had been mild. Drug resistance to sulphonamides among streptococci was unusual, and hypochondriasis had not been encountered. The cost of prophylaxis with sulphonamides was 1·6 pennies per day, and with penicillin 3·8 pennies per day. It was concluded that there was much to be gained and little to be lost from offering prophylaxis to all children with rheumatic fever.

PROFESSOR A. A. MONCRIEFF asked whether the patients had been treated in their own homes or in institutions. The risk was much greater in the latter, and the effects of prophylaxis more obvious. He also asked whether the treated patients and the control patients had been observed over the same period of time; for there were fluctuations in the incidence of rheumatic fever from year to year, and with the general reduced incidence today this might make a considerable difference when numbers were small.

DR. JOHN MARSHALL asked whether any observation had been made on the relapse rate of chorea.

PROFESSOR C. BRUCE PERRY supported the argument for the prevention of streptococcal infection in patients with rheumatic fever. Since the introduction of routine prophylaxis for children in a hospital school for rheumatic fever, the length of stay had been materially reduced as a result of eliminating recurrences and relapses of rheumatic fever during convalescence.

DR. B. E. SCHLESINGER asked how long prophylaxis should be continued.

In reply, DR. THOMAS said that, though the two groups of cases were not started concurrently, they overlapped for three to four years, and the recurrence rate was static in each group over the period. The majority of the children returned home to a normal school life. He was uncertain whether prophylaxis had reduced the length of stay in hospital, but he thought it had. He had no figures regarding the recurrence rate of chorea. He advised prophylaxis up to the age of 20.

9. DRS. D. A. J. TYRRELL and B. SNELL (introduced by PROFESSOR C. STUART-HARRIS) described their *Clinical and Aetiological Studies of Aseptic Meningitis*. They stated that only a small fraction of cases of aseptic meningitis was due to those infectious agents for which laboratory tests were commonly made, namely leptospira, mumps, and lymphocytic choriomeningitis virus. Forty patients admitted to Lodgemoor Hospital, Sheffield, in 1954 had been studied clinically and by attempting virus isolation from faeces and cerebrospinal fluid in tissue cultures and suckling mice. Fifteen out of 16 patients with paralytic poliomyelitis were shown to be infected with polio virus. Only 10 of 24 patients with aseptic meningitis showed any evidence of infection with polio virus. Complement fixation tests indicated that infections with Coxsackie A and B and herpes simplex viruses were probably not causing the illnesses. In 1956 an epidemic of an apparently new disease had occurred. It affected children under 10 and their parents. There were often multiple cases in affected families. In a typical case the patient had a febrile illness with headache and vomiting, followed by a rash which affected the face. It was purplish-red, blotchy, and slightly raised, and in half the cases appeared also on the trunk, where it looked like German measles. There was widespread lymphadenopathy. Small painless lesions of the buccal mucous membrane occurred in a quarter of the cases. There were signs of meningitis, and an increase of lymphocytes and protein in the cerebrospinal fluid. Of 34 patients in 12 families, seven had this typical illness. Three had meningitis only, 12 had rash only, and 12 had a mild non-specific febrile illness. The virus apparently causing these cases was a Coxsackie A virus serologically related to ECHO virus type 9, and had apparently caused similar outbreaks elsewhere in Europe and North America.

SIR RUSSEL BRAIN asked whether a systemic leucocytosis had been observed in these cases.

PROFESSOR ALAN MONCRIEFF asked whether there was any evidence of mouse infestation in the homes from which the patients came. The early workers on this subject (for example the late G. M. FINDLAY) had spoken of the disease as 'mouse meningitis'. There were big administrative problems in deciding whether or not a child had this type of disorder or a non-paralytic poliomyelitis. He asked if there was any quick way of differentiation in a virus laboratory. Another clinical problem was to distinguish between aseptic meningitis and tuberculous meningitis when the organism was not seen, and he thought that a low sugar level in the cerebrospinal fluid was most useful as indicating a bacterial origin.

PROFESSOR STUART-HARRIS wondered whether the syndrome of aseptic meningitis and a rash could be regarded as a 'new' disease or not. It had certainly seemed to be a new phenomenon to those working in the hospitals where the patients were admitted. The present phase of virus work was a difficult one for the clinician, who deserved the fullest sympathy. A jungle of viruses with neurotropic properties had now been revealed in the alimentary tract. Their relation to clinical events was only just becoming discernible.

PROFESSOR JOHN CROFTON said that he had seen an epidemic, somewhat similar to that described, in a ward for tuberculous children about two years ago. Standard virus serological tests had been undertaken without revealing the cause. Naturally the occurrence of such symptoms in children who already had tuberculosis had given rise to a certain amount of alarm. He mentioned herpes zoster as another condition which might give rise to an aseptic meningitis, the meningitic symptoms developing before the skin lesions. Although the lowered sugar level was helpful in differentiating these conditions from tuberculous meningitis at the time when a difficult diagnosis presented itself, the sugar, in a case of tuberculous meningitis, was sometimes very little diminished. His own bacteriologist, by being prepared to examine a cerebrospinal-fluid smear for up to two hours, succeeded in finding tubercle bacilli on smear in 90 per cent. of cases. This of course was an enormous help in diagnosis.

DR. F. F. KANE emphasized the need for confident diagnosis of patients with aseptic meningitis. In attempting to distinguish tuberculous meningitis from virus conditions by a fall in the level of sugar in the cerebrospinal fluid he stressed the necessity for simultaneous estimation of the blood-sugar, and commended Somogyi's copper method as removing several fallacies. In cases of lymphocytic meningitis of virus origin, the possibility of polio virus infection must cause anxiety, and when the patient came from a boarding school or similar institution quick but reliable virology was needed. In Belfast it was now possible to have a provisional virus-culture report within 24 hours of submitting a sample of faeces from the patient, either incriminating or excluding polio virus. This information was of great value in determining the need for precautions among contacts.

In reply to the discussion, DR. TYRRELL said that no leucocytosis had been seen. A low cerebrospinal-fluid sugar level in aseptic meningitis suggested that the case might be tuberculous, and a thorough search for acid-fast bacilli should be made. He thought that epidemics of rash and meningitis might be appearing now because, owing to better hygiene, infection with faecal viruses occurred in older children than previously. In this age-group the clinical picture might be clear-cut, and an increase in prevalence of the virus would produce a recognizable epidemic. Mice only transmitted lymphocytic choriomeningitis.

10. DRS. CHARLES S. DAVIDSON (introduced), SHEILA SHERLOCK, W. H. J. SUMMERSKILL, M. D. TURNER, and STANLEY J. WOLFE (introduced) contrasted the clinical, radiological, biochemical, and haematological findings in *Hepatic Cirrhosis in the Alcoholic and Non-Alcoholic*. Thirty-five chronic alcoholic patients with cirrhosis from the Boston City Hospital were compared with the same number with 'cryptogenic' cirrhosis from Hammersmith Hospital, all seen consecutively in the same period. Striking differences had existed in the clinical course of the disease. The alcoholic cirrhotic patients, who were usually male and aged over 30, had shown a high incidence of deep jaundice and ascites, whereas portal hypertension with gastrointestinal haemorrhage had been the prominent complication in the non-alcoholic. In this group the age incidence had been more even, and female patients had predominated. Hepatomegaly had rarely been as great in the non-alcoholic as in the alcoholic patient, although the incidence and degree of splenomegaly had been strikingly greater in the non-alcoholic. The frequent findings of Dupuytren's contracture, parotid enlargement, and gynaecomastia had been confined to alcoholics, who also had exhibited nutritional and other alcoholic stigmata. Clinical findings, liver biopsies, and liver-function tests indicated that the alcoholic had the greater capacity for recovery, if adequate nutrition and alcohol withdrawal could be enforced; in contrast, the course of the non-alcoholic patient was subject to fewer fluctuations and progressed steadily. A high polymorphonuclear leucocytosis was associated with relapses in the alcoholic, while leucopenia, thought to be related to the splenomegaly, was often found in the non-alcoholic. The degree of anaemia was comparable in both groups, but in the alcoholic patient it was more often macrocytic or iron-deficient. These features, it was suggested, were valuable in determining the aetiology of cirrhosis. A correct diagnosis was important for both prognosis and treatment, and the patient's confessed alcohol intake was often unreliable.

PROFESSOR E. J. WAYNE pointed out that the numerical differences between the two groups were sometimes rather small, and asked whether any tests of statistical significance had been used.

PROFESSOR R. PLATT asked first, whether the development of cirrhosis always followed a period in which the patient's diet had been deficient or whether cirrhosis could develop in alcoholics who had taken a good protein diet throughout; and second, whether there was any evidence as to how quickly cirrhosis could develop. It was common belief that it was the result of many years of intemperance, but he felt that there was little if any evidence for this belief, and that it was possible that cirrhosis really developed quite quickly when the alcoholic began to reject his diet, and not before.

DR. E. G. L. BYWATERS asked whether Dupuytren's contracture in these patients was more frequent unilaterally (in the glass-raising hand) or whether it was, as usual, bilateral.

DR. S. R. F. WHITTAKER asked whether cirrhosis could follow a period of three years' starvation while the patient was a prisoner of war in Japan. He had a patient with this experience who had not suffered from infective hepatitis and was now applying for an army pension.

DR. BODLEY SCOTT recounted a similar case.

DR. B. SCHLESINGER asked whether the gynaecomastia seen in cirrhotics was due to failure of the liver to metabolize oestrogens.

In reply, DR. SUMMERSKILL agreed that the number of patients was inadequate for statistical purposes, but he stressed that the cases were representative of larger numbers seen in both Boston and London. The speed of development of cirrhosis was uncertain, but in some patients, particularly after heavy drinking 'sprees', the histological appearances associated with liver failure were remarkably acute. It was impossible to assess the relative contribution of malnutrition and alcohol to the genesis of cirrhosis, as one rarely occurred without the other, but very heavy drinking and severe food deprivation were probably necessary. In the absence of alcoholism, cirrhosis associated with malnutrition was very rare in Europe, even in prisoners of war, in contrast to its prevalence in Africa, Asia, and elsewhere. Some degree of Dupuytren's contracture had been found in over 60 per cent. of male alcoholics with cirrhosis, and the incidence in male alcoholics without evident liver disease was twice that of the non-alcoholic in Boston. The contracture was found in about the same numbers bilaterally as in the right or left hand. Gynaecomastia was rarely related to the severity of liver disease, but usually improved during recovery, thus suggesting that it might have a nutritional basis.

11. DR. E. B. FRENCH, in a communication on *Biliary and Renal Colic*, commented on the lack of general appreciation that in most of these attacks the pain was constant. The case of a young woman with intermittent pains, which proved to be due to gall-stones, had led to an inquiry into the frequency of different pain patterns. The case histories taken personally from 50 patients with biliary colic, and 50 histories of renal colic obtained by Mr. W. A. T. Robb, had been analysed. Methods for assessing the accuracy of the history and diagnosis were given. In biliary colic the intensity of pain at the onset was variable. In about two-thirds of the patients the pain had increased steadily, over a range of 15 minutes to several hours, to reach a maximum. In 15 cases the pain had been greatest at the onset. At its maximum the pain had remained constant in 46 cases before passing off gradually, or sometimes abruptly. One patient had had intermittent pain throughout, while three had had temporary accentuations of severe background pain. Stone in the common duct could cause a recurrence which was identical with pre-operation pain both in character and distribution. The pattern of renal colic had differed in three respects only; pains of gradual onset had reached their maximum more rapidly; more patients (20) had felt waves of pain lasting 10 to 30 minutes superimposed on severe background pain; no instance of intermittent pain had occurred.

DR. HENRY HOWAT asked how pancreatic pain had been excluded from the series in which biliary pain had been studied, and whether the duration of pain had proved to be significant in distinguishing biliary pain from pancreatic pain.

DR. AVERY JONES asked for details of the distribution of pain of biliary colic, and commented on the frequent absence of radiation to the back.

DR. R. W. LUXTON asked how often prolonged substernal pain simulating myocardial infarction had occurred in cases of biliary colic.

In reply, DR. FRENCH stated that pancreatic disease had been excluded only by the findings at operation and the results of treatment. The right side of the back was rarely the main site of the pain, but was an area of reference in 18 cases. The epigastrium was the main site of pain in 34 cases, in 10 of which there was no radiation. Substernal pain had been infrequent.

12. DRS. A. DOIG (introduced), J. J. R. DUTHIE, R. H. GIRDWOOD, and J. KNOX (introduced) reported the *Response of Megaloblastic Anaemia to Prednisolone*. The unexpected finding of a megaloblastic anaemia responding to prednisolone in a patient who was being treated for rheumatoid arthritis had led to the investigation of the effect of prednisolone in other patients with untreated megaloblastic anaemia. These patients had included four with Addisonian pernicious anaemia, two with coeliac disease which had persisted into adult life, two with an unusual form of megaloblastic anaemia associated with rheumatoid arthritis, and one who developed megaloblastic anaemia after partial gastrectomy. Malabsorption of folic acid had been demonstrated in the patients with coeliac disease, while the others had been shown to have vitamin-B_{12} deficiency. A haematological response,

with conversion of the bone-marrow to normoblastic erythropoiesis, had been obtained in eight of the nine cases. This response had differed in several respects from that which followed treatment with cyanocobalamin or folic acid. There was a slower rise in the red-cell count and haemoglobin level, the reticulocyte peak was usually suboptimal, and an immediate fall in serum-iron level did not occur. During the administration of prednisolone there was no significant alteration in the vitamin B_{12} level in the serum. Evidence against prednisolone possessing intrinsic-factor activity was its effectiveness in the cases of folic-acid deficiency, its failure to improve the absorption of labelled cyanocobalamin in a patient with pernicious anaemia, and its failure *in vitro* to behave like intrinsic factor. Microbiological assay of the prednisolone tablets gave no indication that they contained folic acid or vitamin B_{12}.

THE PRESIDENT drew attention to the danger of suppressing the haematological evidence of unsuspected megaloblastic anaemia when treating other conditions with prednisolone; in such instances neurological complications might be precipitated.

13. DR. M. A. PEARS (introduced) and PROFESSOR G. W. PICKERING described *Neuroretinopathy in Gastrointestinal Haemorrhage*. Dr. Pears said that while blindness and optic atrophy were well known to follow severe haemorrhage, particularly from the gastrointestinal tract, it appeared much less well known that transitory retinal lesions, unaccompanied by visual symptoms, could be observed during the course of profuse haemorrhage. He showed slides illustrating the clinical course of five patients suffering from massive gastrointestinal bleeding in whom such lesions, consisting of papilloedema, haemorrhages, and exudates, either together or separately, had been observed. Photographs or paintings of these lesions were shown, together with others of the same fundi a few weeks later when the appearances had returned to normal. The lesions closely resembled those of hypertensive neuroretinopathy, and could be distinguished from them only by the fact that the vessels in the affected fundi were normal in appearance. In two of these cases it had been possible to observe that the development of the lesions closely followed a short but profound fall in blood-pressure, which was quickly reversed by accelerating the transfusion rate. In them at least it appeared unlikely that these lesions were due to a brief period of ischaemic anoxia.

PROFESSOR J. MCMICHAEL said that in chronic anaemia the development of retinitis appeared when the haemoglobin was below 30 per cent. At this stage there were gross cardiovascular changes, including high cardiac output with peripheral vasodilatation. After acute haemorrhage, however, both retinitis and elevated cardiac output could develop with haemoglobin levels as high as 60 per cent. It seemed probable that retinal changes were correlated with haemodynamic disturbances rather than the haemoglobin level. He thought some of the illustrations showed general retinal oedema rather than true papilloedema.

DR. GILBERT HALL commented on the apparent absence of the changes of papilloedema in two of the fundus pictures that were shown, and suggested that the appearance might be more correctly designated as neuroretinitis.

DR. AVERY JONES mentioned two patients he had seen in whom there had been visual disturbance after brisk bleeding from duodenal ulceration, one having permanent telescopic vision in his one remaining eye. It was a complication associated with recurrent bleeding in an already exsanguinated patient, and probably due to the reactive vasoconstriction damaging the retina. He emphasized the importance of vigorous transfusion and timely surgery in the management of these cases.

In reply, DR. PEARS said that retinal oedema had not been noticed. The appearance was probably a photographic artifact. True papilloedema had occurred in three of the five cases.

14. DRS. B. H. MCCRACKEN and F. M. PARSONS (introduced by PROFESSOR R. E. TUNBRIDGE) referred to their *Clinical Experience and Indications for the Use of the Artificial Kidney*. A Kolff type of artificial kidney had been used to perform 43 dialyses in 30 patients. The hazards of the procedure had been small. A six-hour dialysis had largely reversed abnormal chemical findings in the plasma, and clinical improvement had usually followed 24 to 48 hours later. Disappointing results had been obtained in chronic nephritis, but dialysis had been regarded as worth while in order to enable diagnostic procedures to be performed in uraemia of uncertain cause and in the treatment of extrarenal uraemia and tubular necrosis, in patients referred from a wide area, after control by standard dietary treatment had failed. Failure had been judged by general clinical deterioration and plasma-potassium levels rising above 7 mEq. per litre with alkali reserve falling below 13 mEq. per litre. Five patients had survived and seven had died. A review of cases of tubular necrosis, including cases managed successfully without dialysis, suggested that individual variations in the rate of catabolism were most important in determining clinical severity. Cases could be

graded in severity according to daily increase of blood urea-nitrogen on dietary management: mild cases (< 15 mg./100 ml. per day) could usually be controlled without dialysis, whereas moderate (15 to 30 mg./100 ml.) and severe cases (> 30 mg./100 ml.) would usually require dialysis for the patient's survival. The most severe cases were those in which factors such as infection were present in addition to kidney disease. These other factors were usually the cause of death in fatal cases. It was concluded that the artificial kidney had a part to play in the treatment of selected cases of acute uraemia.

Dr. J. R. Elkinton (introduced) described his experience at the University of Pennsylvania with his colleagues, Drs. Bluemle and Webster. They had treated 77 patients with acute tubular necrosis, of whom one-half had had at least one dialysis. Their mortality rate (just over 50 per cent.) had been affected by the reference to them of many patients with serious complications such as haemorrhage, infection, and cardiac failure. Sufferers from rapid catabolic states, such as injuries, burns, infection, and extensive surgery, deteriorated rapidly, but benefited greatly from dialysis. Improvement was often dramatic, but clinical impressions of benefit were not proof. Biochemical demonstration of noxious substances that could be removed was required. It was difficult to decide where a dialysis equipment should be installed and when it should be used. They regarded increasing hyperkalaemia, and especially rapid clinical deterioration, despite proper conservative management, as the chief indications for dialysis, but judgement was often difficult, and long experience was required.

Dr. R. I. S. Bayliss asked what conditions were associated with a very rapid increase of urea nitrogen. It was important to know this, because it was in patients with these conditions that the artificial kidney was most likely to be needed. His experience had been that a rapid rate of catabolism occurred in anuric patients with a gravid uterus and in patients with uncontrollable infections. It was particularly patients towards the end of pregnancy, with a large mass of uterine muscle to involute, who seemed to get rapidly rising blood-urea levels.

Dr. E. G. L. Bywaters inquired about vomiting, and whether this troublesome complication (which 10 years ago often prevented an adequate application of the Bull-Borst régime, but seemed to respond to dialysis) was not sufficiently controlled nowadays with chlorpromazine, so that the Bull-Borst régime could be more readily applied and dialysis avoided.

Dr. Sheila Sherlock asked whether any cases of hepatic coma had been treated.

Dr. C. L. Cope described a number of cases treated with the French Hamburger kidney in collaboration with Mr. R. Shackman of the Department of Surgery at the Postgraduate Medical School of London. In these cases also, the main indications for use of the machine had been the failure of conservative treatment, leading to clinical deterioration associated with either high serum-potassium levels (three cases), severe acidosis (two cases), or increasing blood-urea and coma (four cases). The uncertainty of diagnosis made it impossible to treat only lesions from which recovery was possible. Lower-nephron nephrosis and cortical necrosis might be clinically indistinguishable, and the cause of a clinical deterioration might also be uncertain. Immediate improvement occurred in most cases as a result of dialysis but, as in Dr. Elkinton's Unit, great caution had been observed in selecting cases. Of nine patients given dialysis, five proved to have irreversible renal damage, while four had died of complications unconnected with the dialysis. Pulmonary oedema had occurred during or after dialysis in some cases.

Dr. K. G. Lowe asked what size of population merited an artificial kidney unit by providing enough clinical material to maintain efficiency in the unit. He also asked for Dr. McCracken's comments on the value of the American Artificial Kidney Centre in the Korean war.

In reply, Dr. McCracken agreed that it was difficult to assess the extent to which dialysis was life-saving in tubular necrosis because of the impossibility of having control series, but it seemed certain that some patients who survived would not have done so without dialysis. The factors which they had most often found associated with excessive catabolism in patients with tubular necrosis, and hence with a poorer prognosis, were involution of the uterus after delivery, surgical trauma, associated liver diseases, and complicating infections. They had not treated any cases of hepatic coma. They felt that dialysis did not of itself influence pulmonary oedema and, although they had treated several patients in this condition, the only one who had shown any deterioration had a low plasma-sodium level, and in retrospect should have had a lower sodium level in the bath fluid than the one used. In judging the size of population which justified an artificial kidney centre, it was difficult to predict the clinical demand that would arise in this country when the results of the machine were widely known. Figures based on the experience of continental countries had suggested one machine for a population

of 10 million, but local geographical difficulty in transfer of patients might also be a factor.

15. DR. O. WRONG (introduced by PROFESSOR R. PLATT), in his communication *Renal Potassium Loss, Hypertension, and Unilateral Renal Disease*, stressed the difficulty of distinguishing between potassium-losing renal disease and potassium loss due to excessive adrenal secretion of aldosterone. He described a 54-year-old man who had developed thirst, polyuria, loss of weight, and weakness, and had been found to have a hypokalaemic alkalosis. Hypertension had been observed many years previously. One of his kidneys had been found to be small, and did not secrete urine; the urine from the opposite kidney had contained large amounts of aldosterone. There had been no clinical improvement with large doses of potassium by mouth, and aldosterone excretion had risen still further. At operation the adrenals had been found to be small, and had not contained a tumour; 90 per cent. of the adrenal tissue, weighing only 5·2 gm., had been removed, and histologically had been essentially normal. The abnormal kidney had also been excised and had shown the histological features of renal ischaemia, with glomerular crowding and tubular atrophy. A biopsy of the contralateral kidney had shown the changes of malignant hypertension only. After operation the patient had lost his symptoms, and his blood-pressure had returned almost to normal. The case was of value in showing that morphologically normal adrenal glands could secrete excessive amounts of aldosterone and cause severe potassium deficiency. He suggested that ischaemic renal disease might stimulate aldosterone secretion (a form of 'secondary aldosteronism'), and recalled evidence from animal experiments of increased adrenal activity in renal hypertension.

PROFESSOR F. T. G. PRUNTY said that the relation of the pathological lesion to the excessive aldosterone production was an important point. He had studied three patients suffering from primary aldosteronism, two having had hypertensive cardiac failure together with renal disease, which might have been secondary in part to the hypertension and in part to the potassium deficiency. One patient had had malignant hypertension. The lesions found had been respectively adrenal cortical carcinoma and a small cortical adenoma with bilateral adrenal hyperplasia; in the last instance the adrenals had been normal. The first and the last patients had excreted excessive urinary aldosterone, the second patient had not. He also mentioned a case of Dr. Edmunds with very bizarre features, namely Addisonian pigmentation, a pre-diabetic state, moderate hypertension, absence of clear-cut signs of Cushing's syndrome, and marked potassium deficiency. This patient had bilateral adrenal cortical hyperplasia associated with large increases of ketosteroids and ketogenic steroids (unresponsive to administered corticotrophin), some excess of aldosterone in the urine and high levels of corticotrophin in the plasma. There seemed to be no good evidence that hypokalaemia and alkalosis could be produced by renal disease, so they were important pointers to primary aldosteronism. A striking feature of the potassium deficiency from this cause was the prompt and significant rise in the level of serum-potassium induced by oral administration of 100 or more mEq. of potassium daily, which could be a potential danger to the patient.

DR. P. FOURMAN described a man aged 32 with malignant hypertension, potassium depletion, alkalosis, and diminished serum-sodium. His hypertension had preceded the depletion of potassium. He excreted increased amounts of aldosterone. His adrenal glands were enlarged; the removal of one of them had arrested his loss of potassium, but the removal of both had failed to alter the course of his hypertension, and he died. Dr. Fourman felt that in this case the hypertension could not be attributed to aldosteronism, and that the reverse might even be true.

DR. S. W. STANBURY had observed two patients with azotaemia and the syndrome of 'salt-losing nephritis' in whom the urinary output of aldosterone remained at about 10 times the average normal value, in spite of a huge daily intake of sodium chloride. In one patient, who had been maintained in apparent external balance of sodium for more than a year, the high output of aldosterone was associated with a normal amount of exchangeable body-sodium and a normal level of serum-sodium. It was suggested that after a prolonged period of physiological stimulation the adrenal production of aldosterone might become autonomous.

In reply, DR. WRONG said that his patient had initially shown a low normal figure for exchangeable potassium (38 mEq./kg.) and increased exchangeable sodium (50 mEq./kg.) at a time when his plasma-sodium level was low (133 mEq./l.). He doubted whether the serum-sodium concentration was of value in distinguishing between 'primary' and 'secondary' aldosteronism, and attributed the hypernatraemia reported in some cases of hyperaldosteronism to a water deficit resulting from failure in renal water conservation.

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